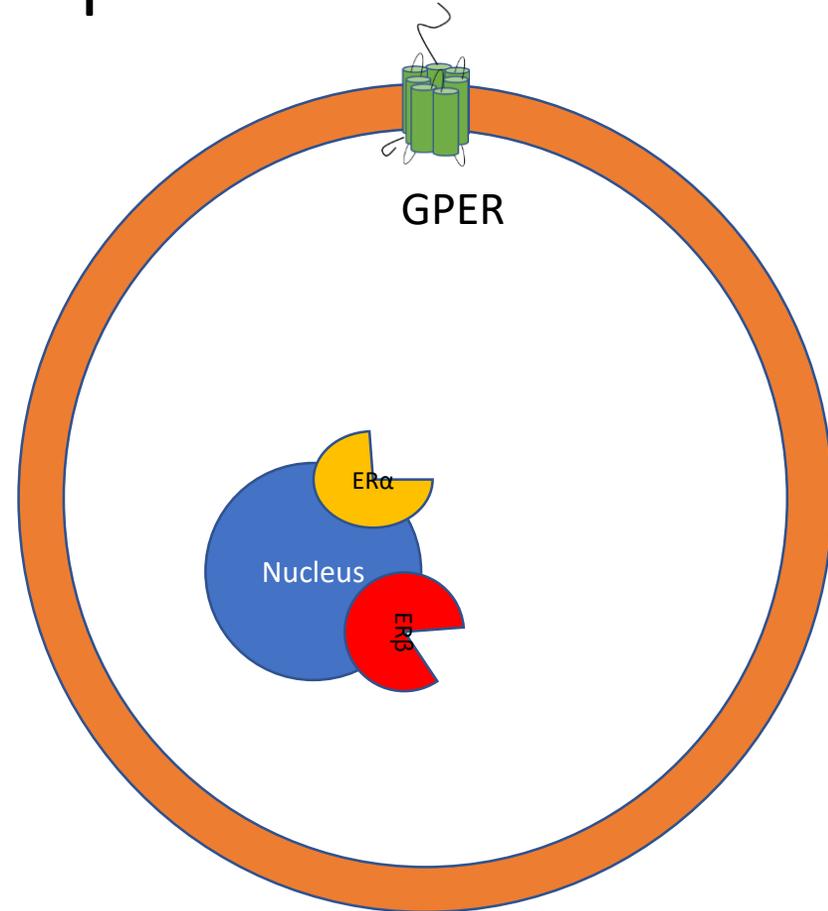
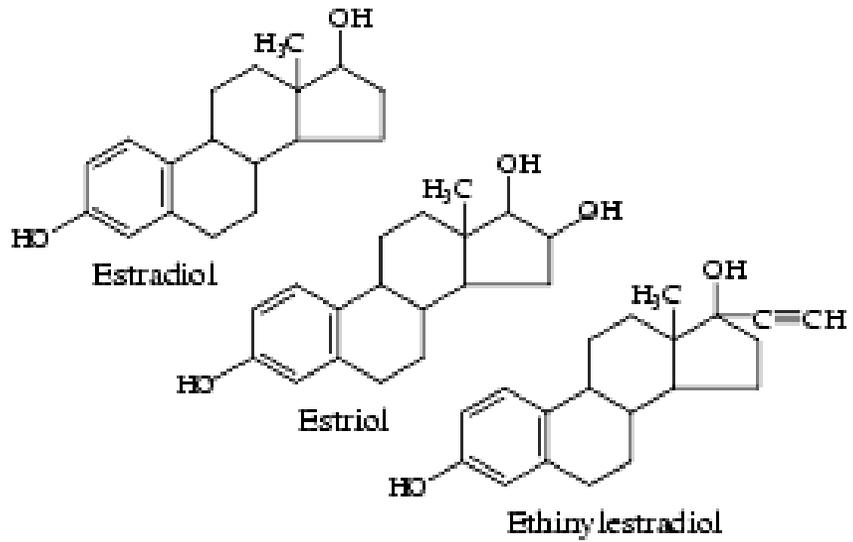


# Estrogen and Brain Development

Kyle Pemberton

# Estrogens and Estrogen Receptors



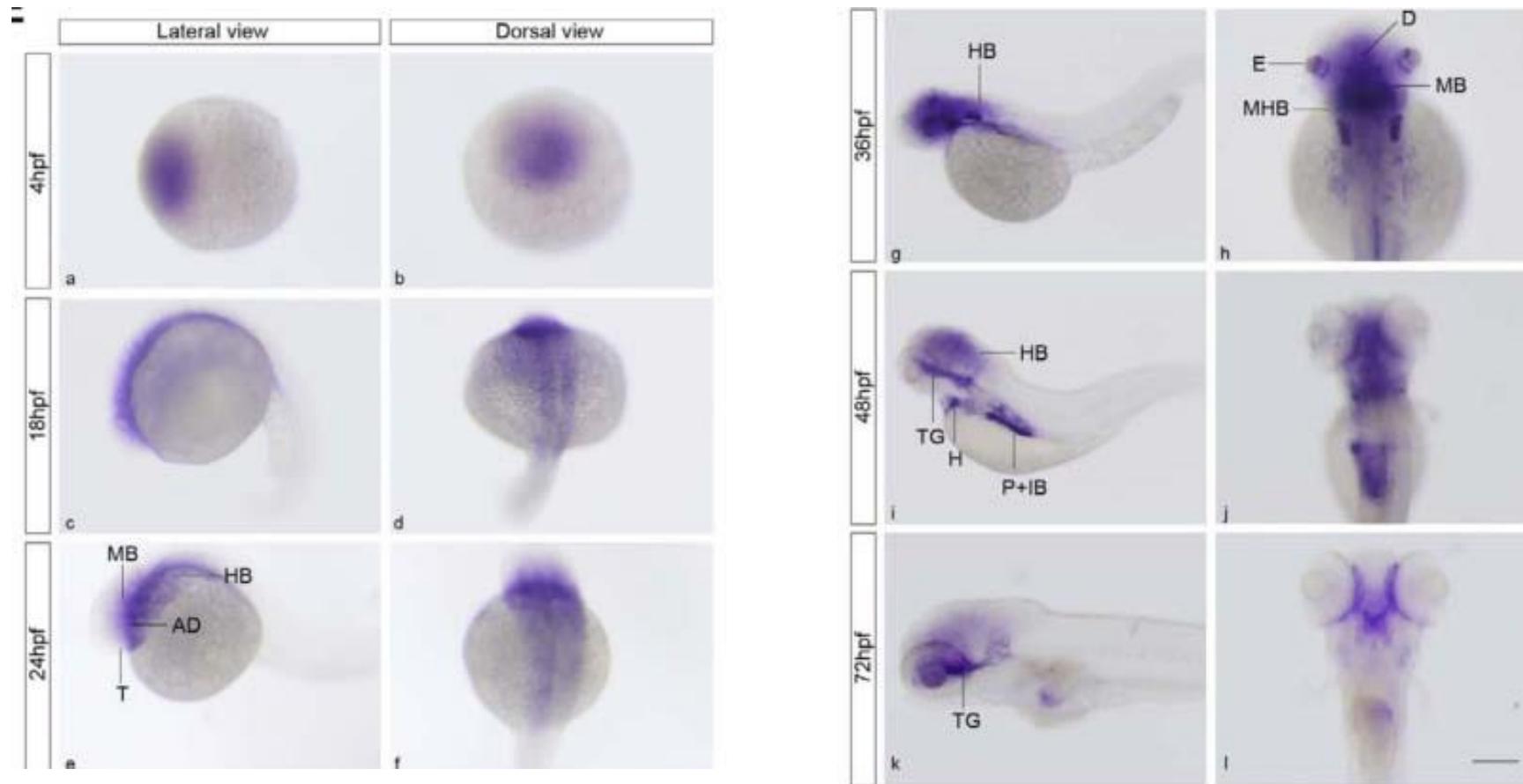
# Estrogen

- Estrogen was shown to enhance brain maturation in the late 1960's (Heim, 1966)
- ER $\alpha$  was the only estrogen receptor known until the discovery of ER $\beta$  in the mid-1990's
- Both of these estrogen receptors are nuclear receptors, but estrogen had been shown to mediate rapid, non-genomic actions associated with G-protein coupled receptors
- The orphan receptor GPR30, cloned in the mid-1990's, officially named an estrogen receptor in 2007

# Embryonic

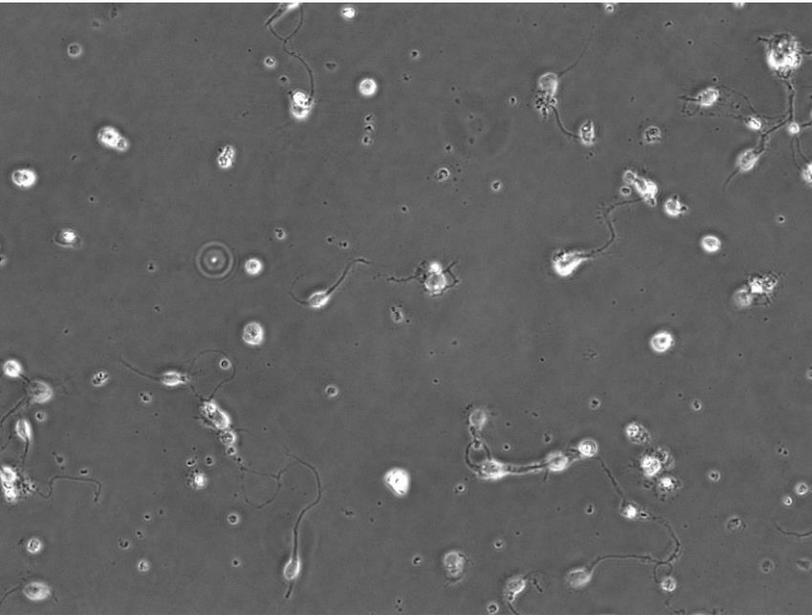
- Estrogens aid in cell type differentiation, proliferation, and survival (Habauzit *et al*, 2011)
- E2 increases release of nerve growth factors (Kanda & Watanabe, 2003)
- High levels of estrogen in the embryonic brain (Konkle & McCarthy, 2011)
  - Specific brain regions have higher levels of estrogens
  - Hippocampus, cortex, hypothalamus
  - Levels drop off steeply after birth
  - Much of the estrogen in these brain areas are produced by cells in the brain

# GPER Distribution in Developing Zebrafish Brain

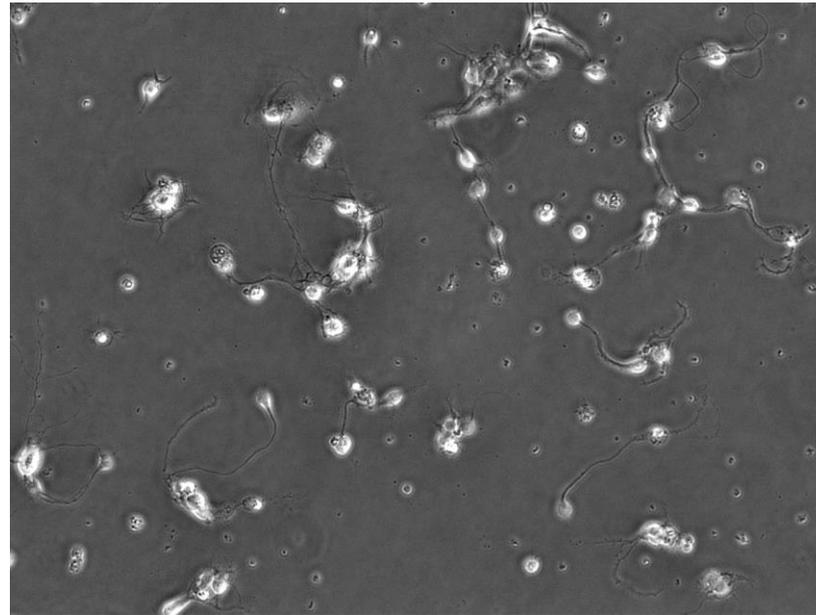


# Estrogen and Embryonic Neurite Outgrowth

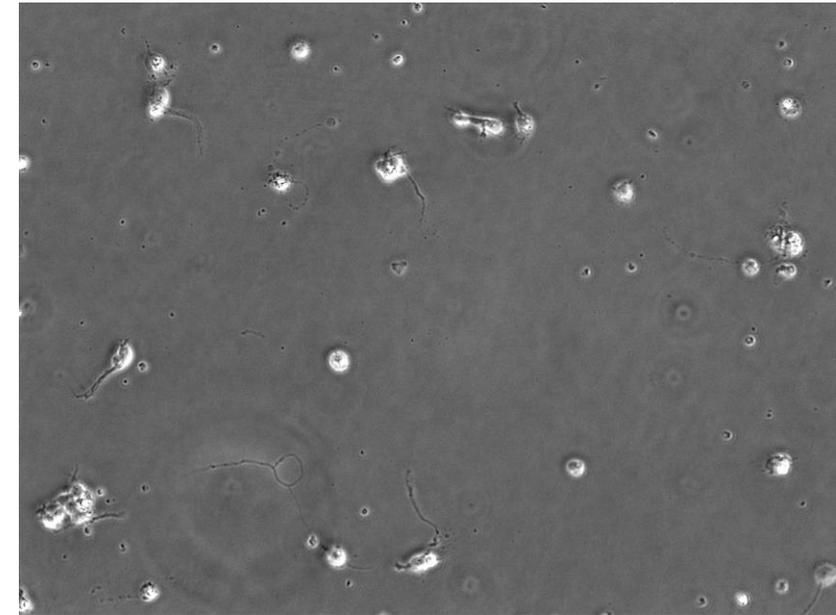
Control



100 $\mu$ M E2



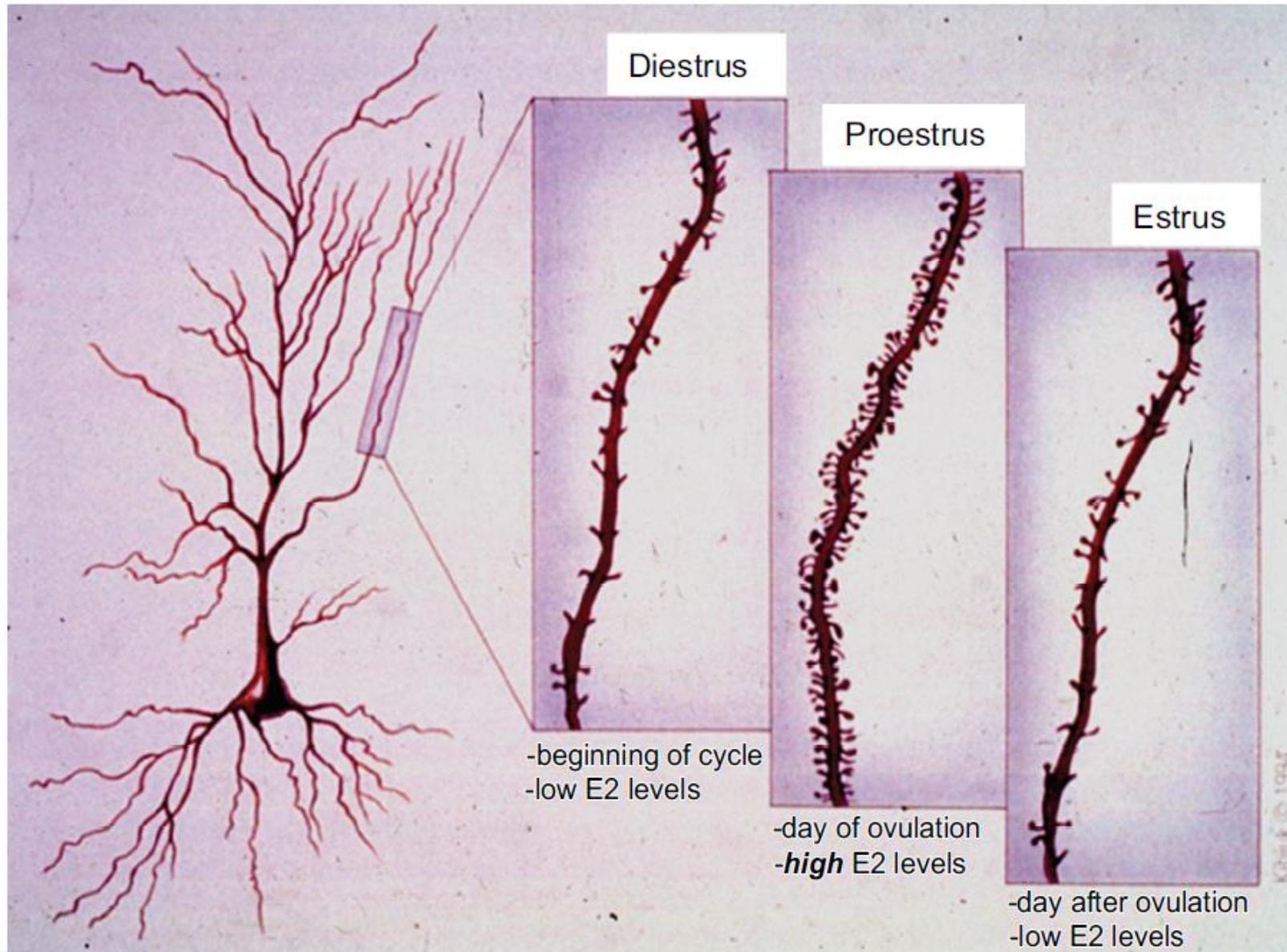
10 $\mu$ M G1 (GPER antagonist)



# Adult and Aged

- Stress conditioning in rats is estrogen related (McEwen and Milner, 2017)
  - Males and females had vastly different responses
  - Difference was abolished with ovariectomized rats
- Estrogens increase dendritic spine and synapse formation (Li *et al*, 2004; Bian *et al*, 2014)
  - Enhanced memory and learning

# Dendritic Spines and Estrogen Levels

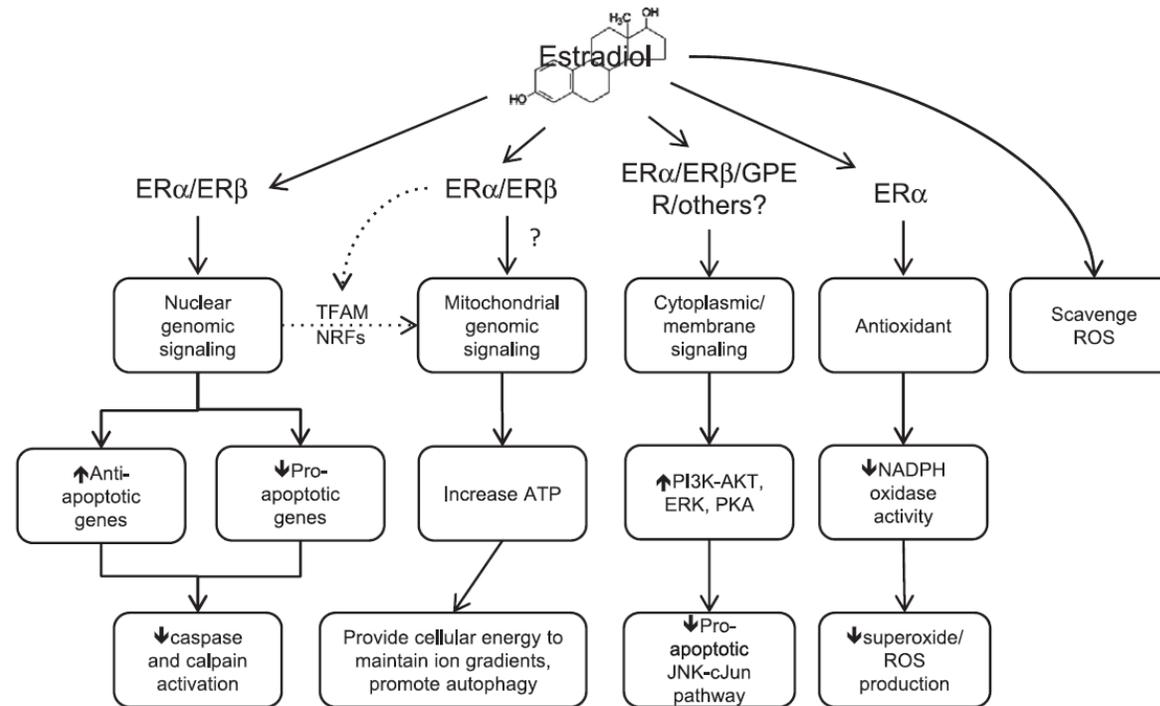


Hara Y *et al*(2015) Estrogen Effects on Cognitive and Synaptic Health Over the Lifecourse. *Phys Rev* 95:785-807.

# Adult and Aged cont.

- Women have better recovery from brain damage (stroke, traumatic brain injury, seizures, etc) than men (Schreihofner & Ma, 2013)
  - Postmenopausal women have similar recovery compared to men
- Estrogen replacement may aid in age related cognition decline in women (Hao *et al*, 2007)
  - Critical period to begin estrogen therapy, may increase chances of dementia or Parkinson's if begun outside that period (Schreihofner & Ma, 2013)

# Estrogen's Neuroprotective Pathways



**Fig. 1 - Summary of the mechanisms of estrogen neuroprotection and the proposed role of estrogen receptors in the protective actions. Estrogen actions on the mitochondria are mediated, in part, through increases in nuclear transcription of the mitochondrial transcriptional regulators mitochondrial transcription factor A (TFAM) and the nuclear respiratory factors (NRFs).**

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