

ACTIVATION OF THE IMMEDIATE EARLY GENE C-FOS BY ACUTE AND REPEATED TREATMENT WITH FLIBANSERIN

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- Flibanserin is a 5-HT_{1A} agonist/5-HT_{2A} antagonist in development for treatment of Hypoactive Sexual Desire Disorder
- Flibanserin increases appetitive sexual behaviors in female rats following repeated daily treatment for 21 days.
- 21 day treatment persistently elevates basal levels of dopamine and norepinephrine in prefrontal cortex
- These region specific changes in monoamines (dopamine and norepinephrine) may induce behavioral changes observed*
- Do changes in gene transcription/protein expression underlie the observed long-term pharmacology?

* Multifunctional Pharmacology of Flibanserin: Possible Mechanism of Therapeutic Action in Hypoactive Sexual Desire Disorder.

Stahl SM, Sommer B, Allers KA. J Sex Med. 2010 Sep 14

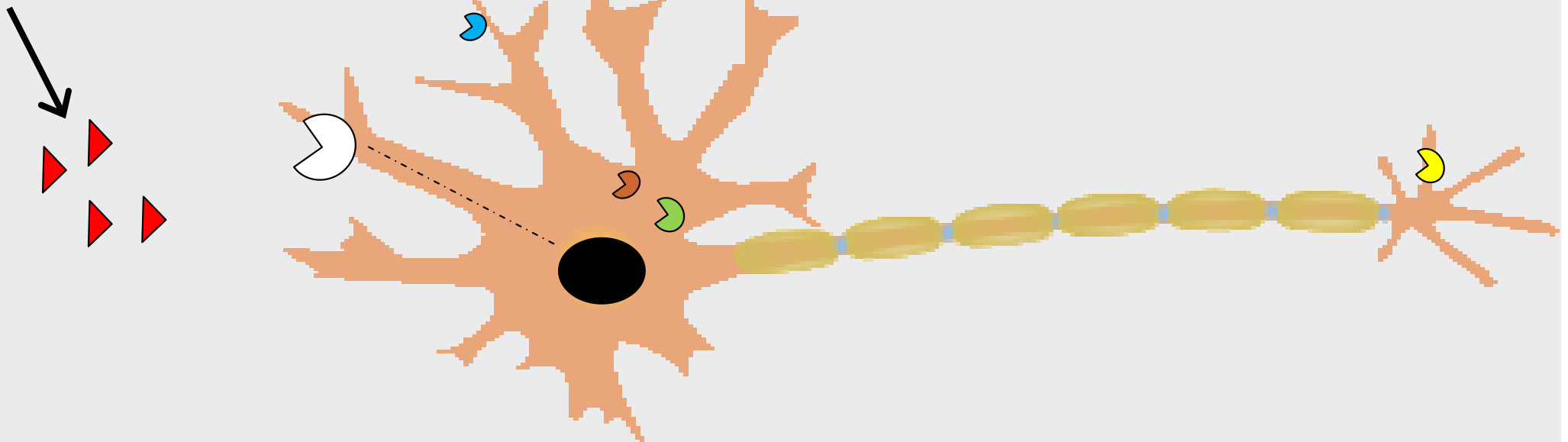
C-fos is an Immediate Early Gene

Expressed in cell nucleus – it's expression is known to lead to gene transcription changes.

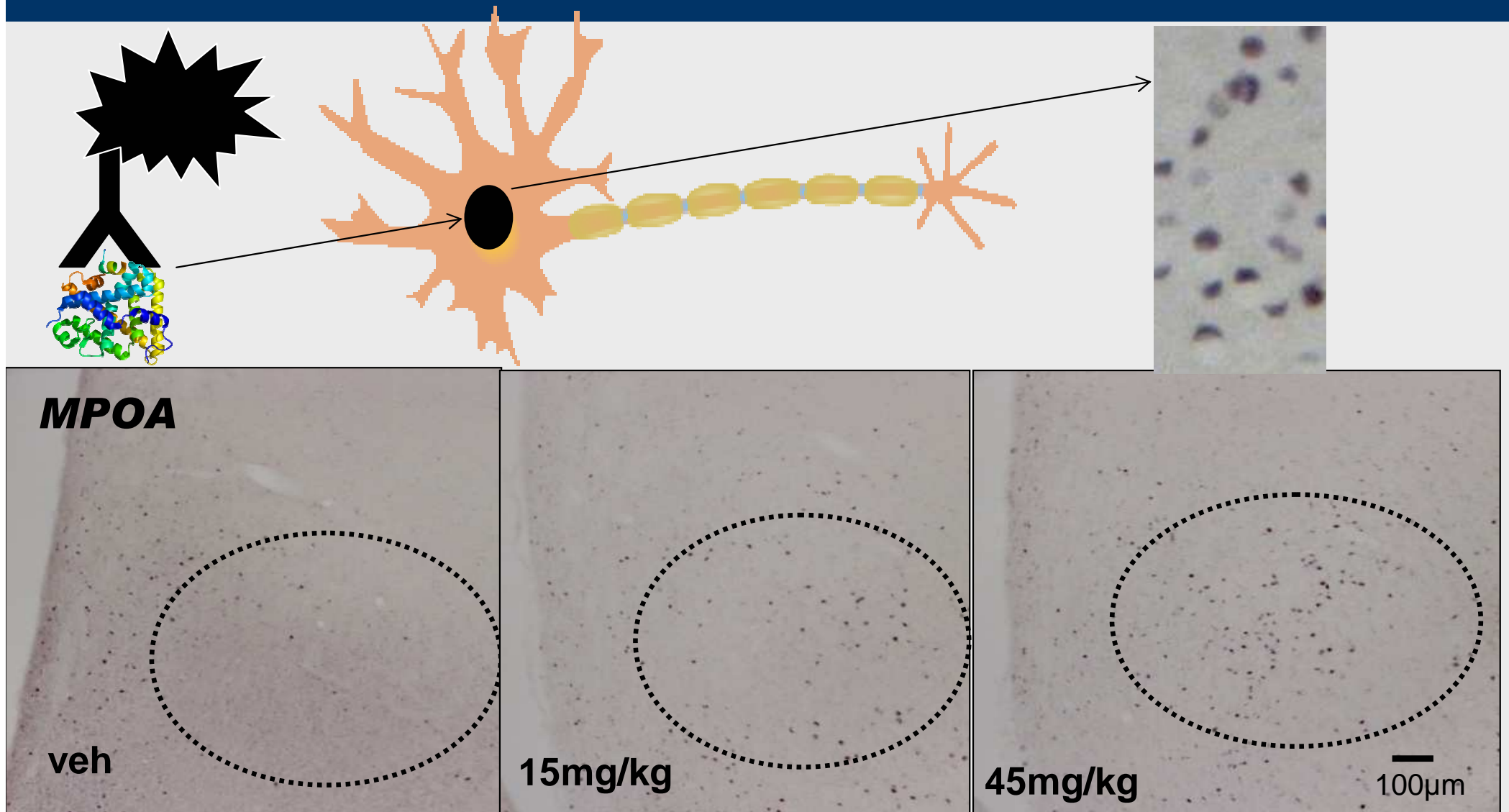
In essence: if a stimulus increases c-fos expression – there will be changes at the genome

C-FOS ACTIVATION 45 MINUTES - HOUR
INTRACELLULAR EFFECTS MILLISECONDS-SECONDS
FURTHER CHANGES IN GENE EXPRESSION-
HOURS/DAYS/WEEKS

FLIBANSERIN

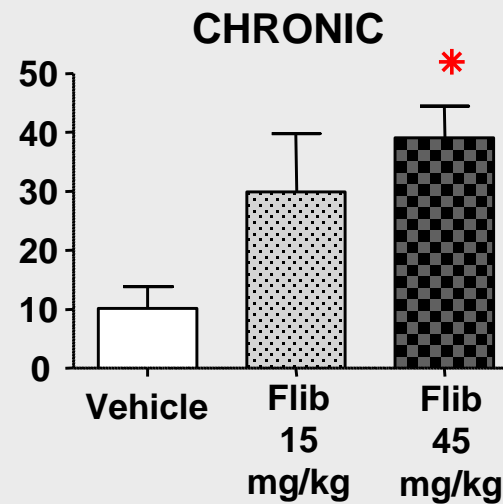
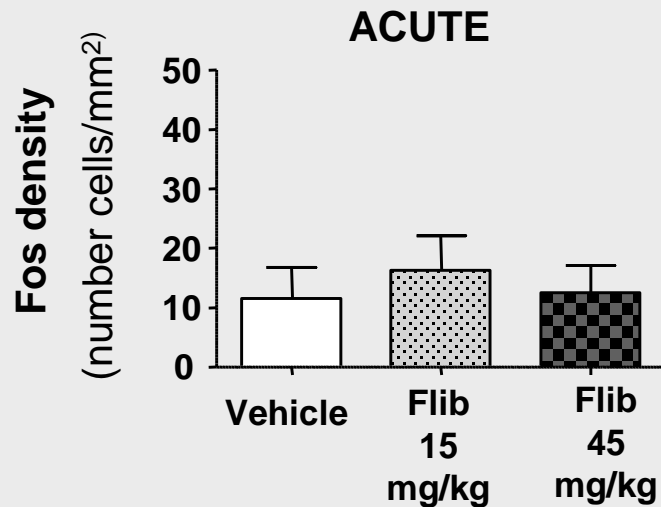


What is c-fos and HOW do we measure it?



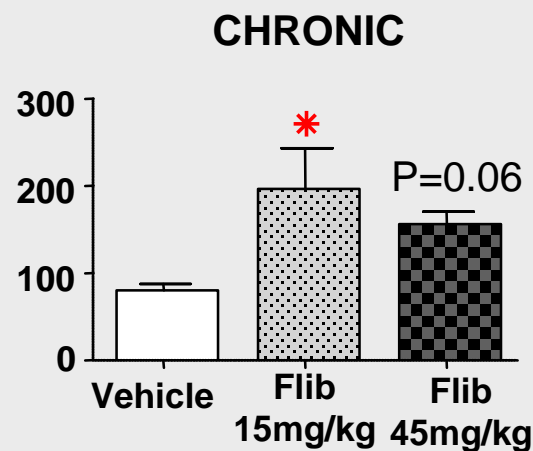
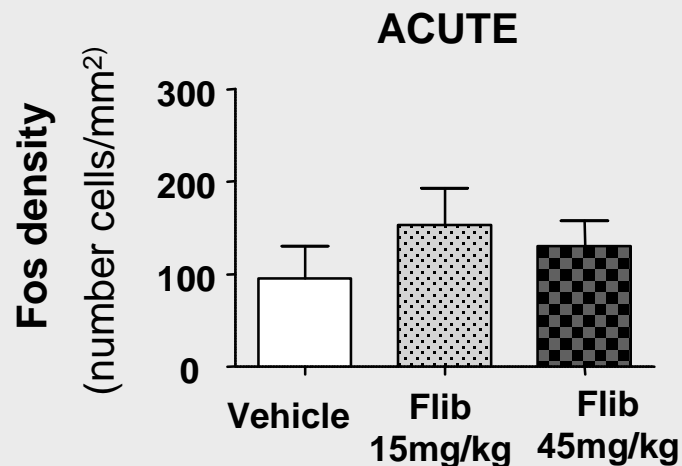
C-Fos expression in the medial preoptic area (MPOA) in females receiving vehicle, Flibanserin 15 mg/kg or 45 mg/kg in chronic (22 days) treatment.

Medial Preoptic Area - Hypothalamus



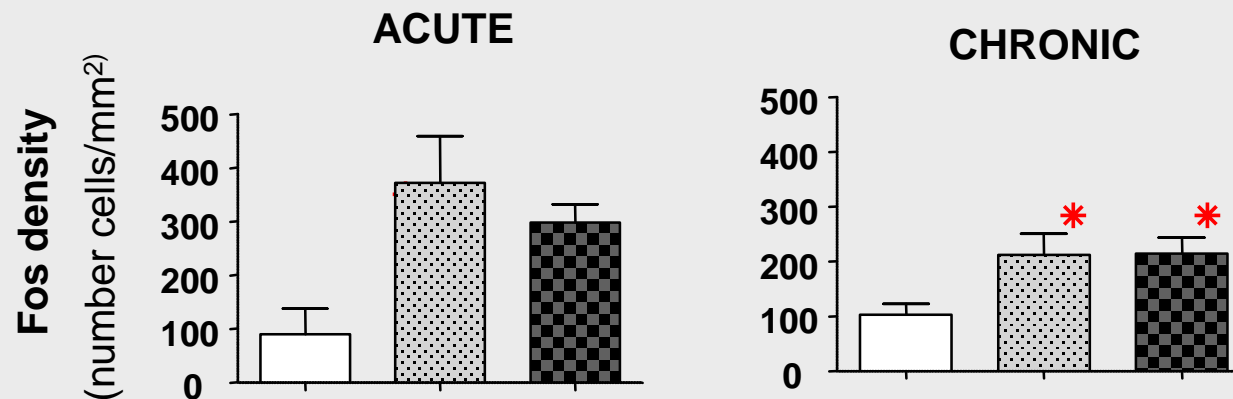
Integration of signals related to sexual desire. Involved in initiation of motivated behavior

Ventral Tegmental Area - Dopamine



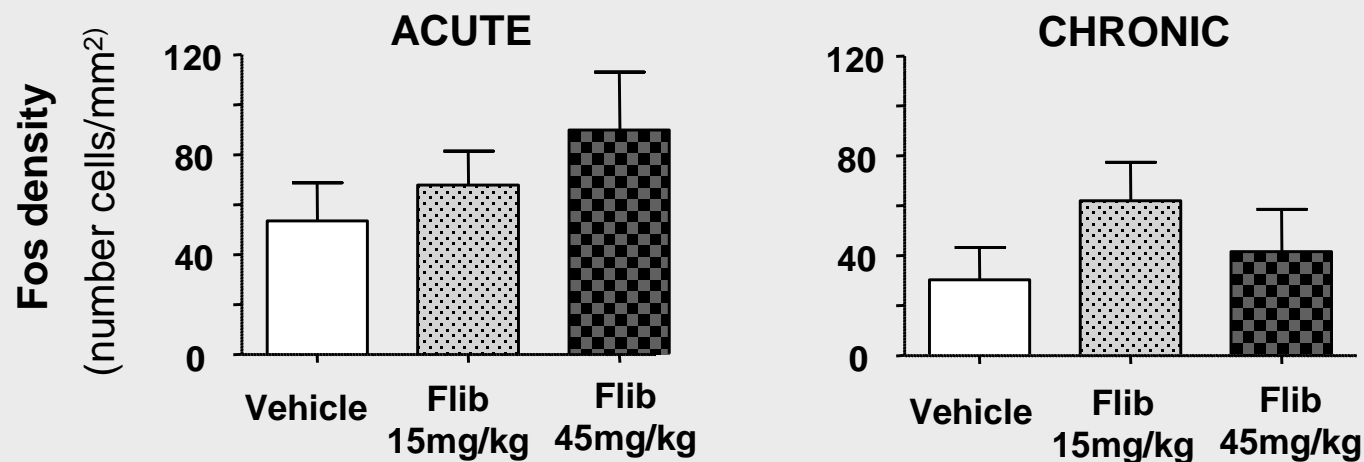
Area which has neurons that contain and release dopamine to mesolimbic/ mesocortical systems.

Locus Ceruleus - Norepinephrine



Area with neurons that contain and release norepinephrine to brain and spinal cord.

Dorsal Raphe Nucleus - Serotonin



Area which has neurons that contain and release serotonin.

- Repeated 21 day treatment of flibanserin leads to persistently elevated levels of dopamine and norepinephrine, with no long term changes in serotonin.
- Repeated 21 day treatment of flibanserin leads to increases of the immediate early gene c-fos :
 - in the neurons that produce dopamine and norepinephrine, but not in those that produce serotonin.
 - in the neurons of the MPOA of the hypothalamus, a region important for integrating signals sexual related to sexual desire

Changes in the gene expression may underlie the altered monoamines following flibanserin treatment and the activation of neurons in the hypothalamus