

Sex Differences in Central Expression and Effects of Brain-Derived Neurotrophic Factor

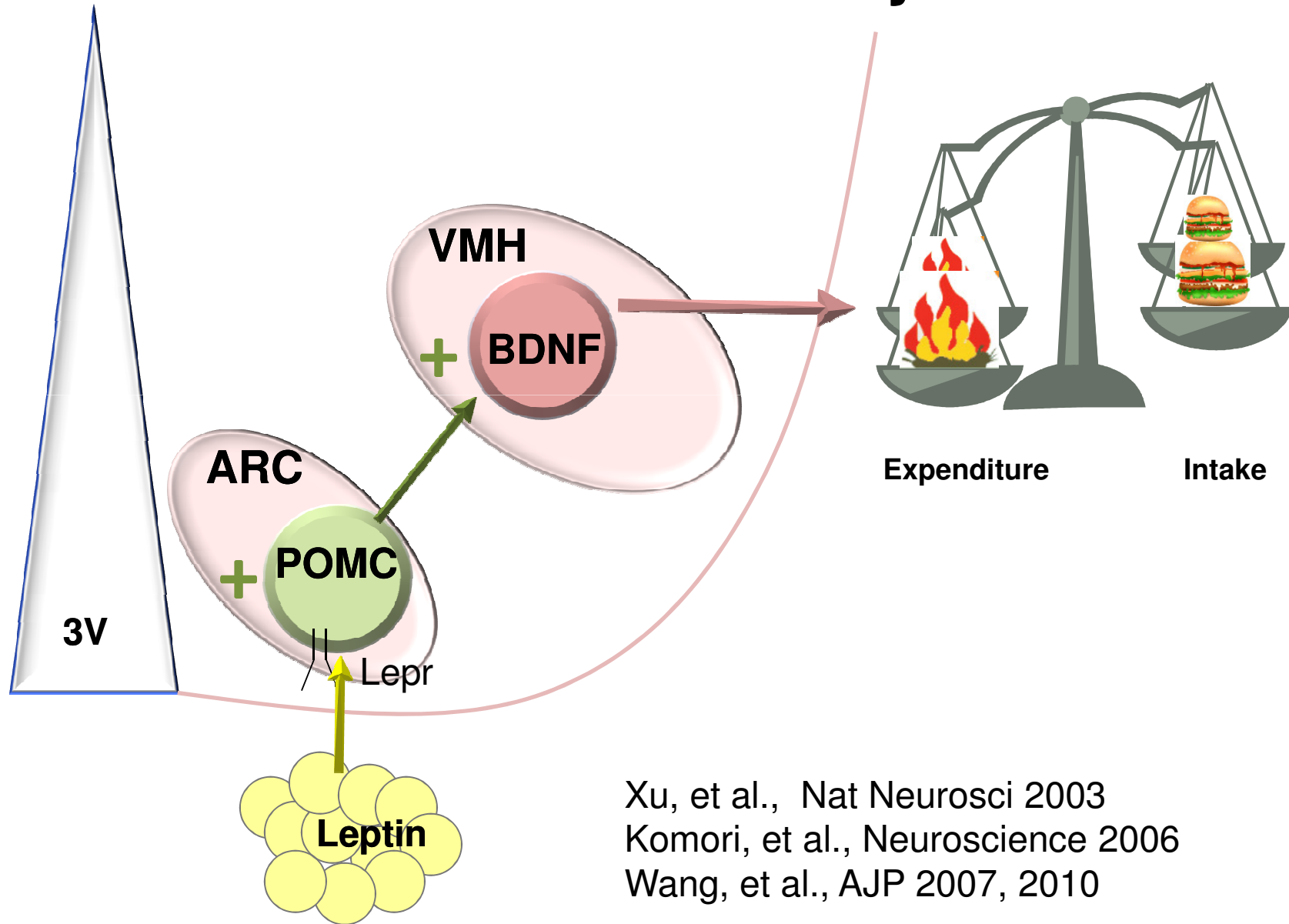
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International Conference on Endocrinology

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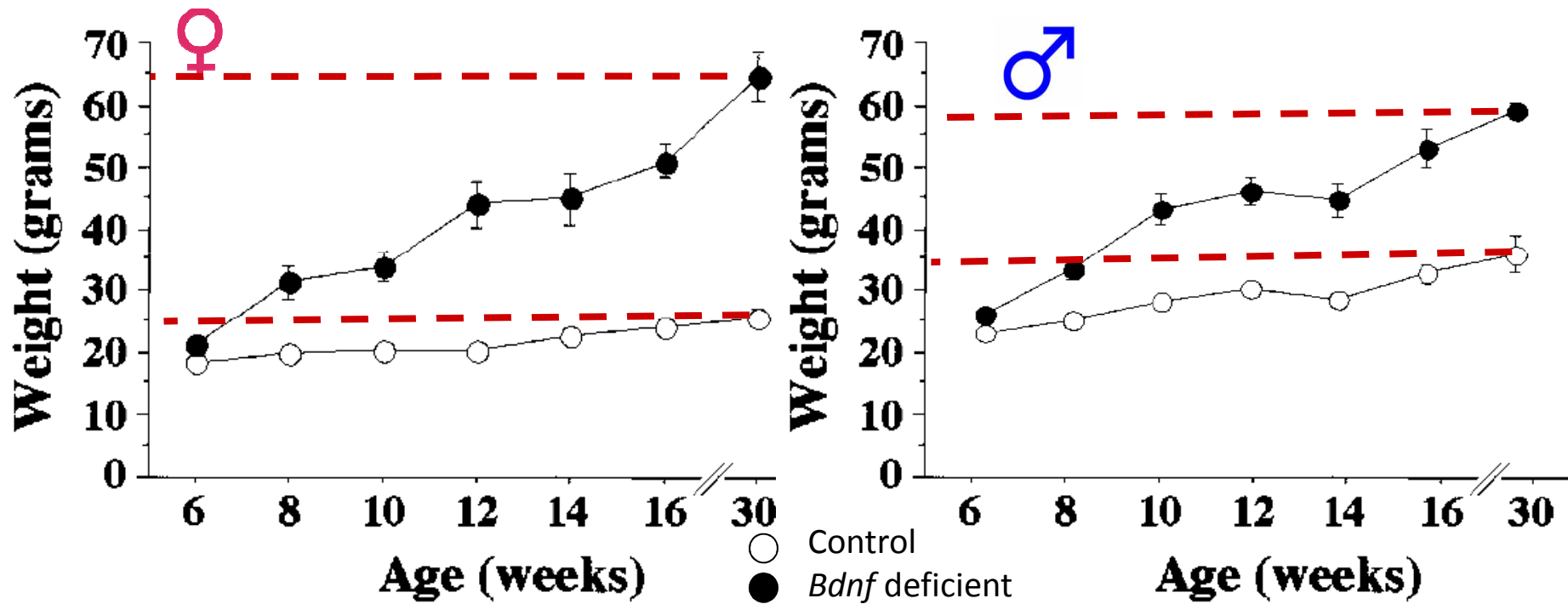
Arcuate melanocortin system



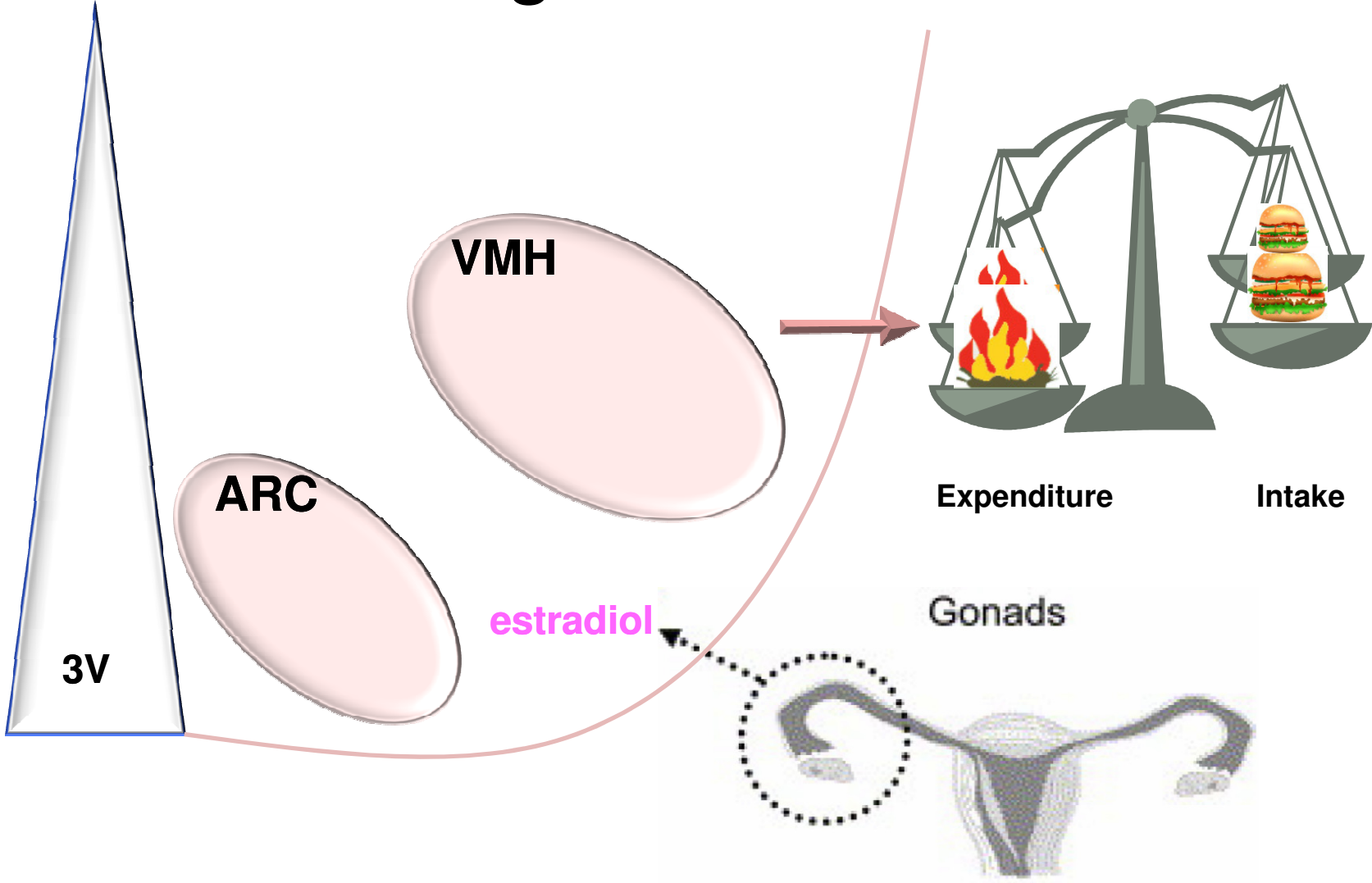
Xu, et al., Nat Neurosci 2003
Komori, et al., Neuroscience 2006
Wang, et al., AJP 2007, 2010

Transgenic mouse models

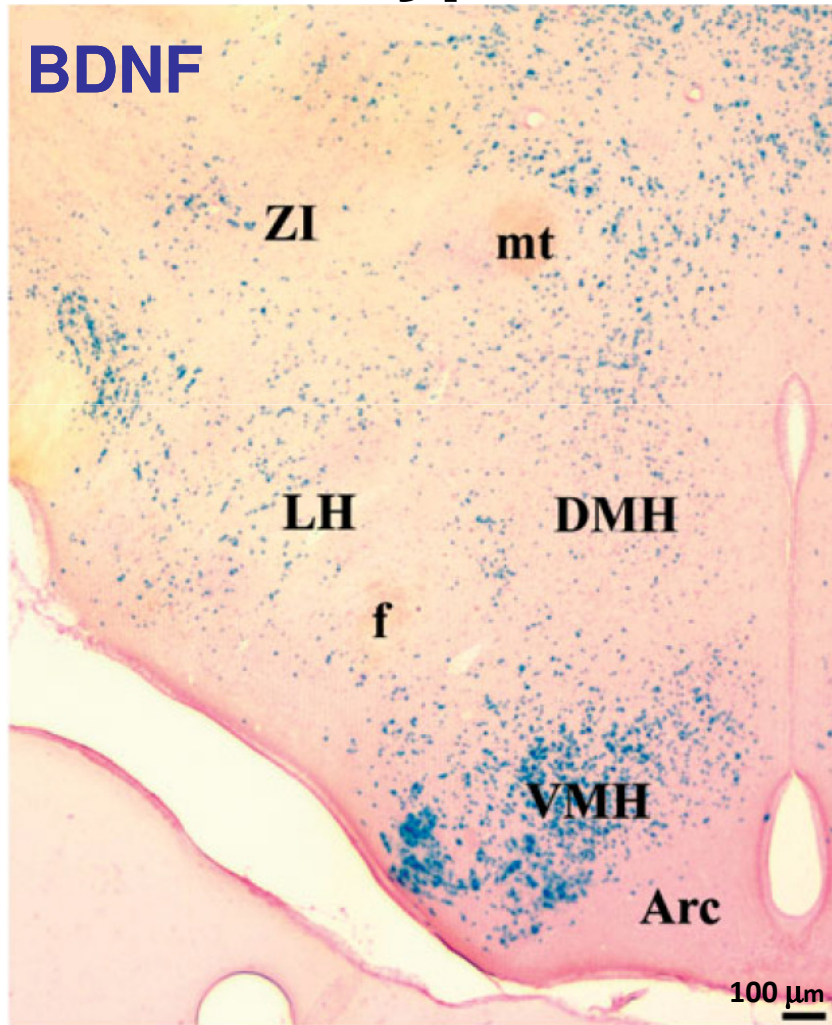
BDNF conditional deficient mice



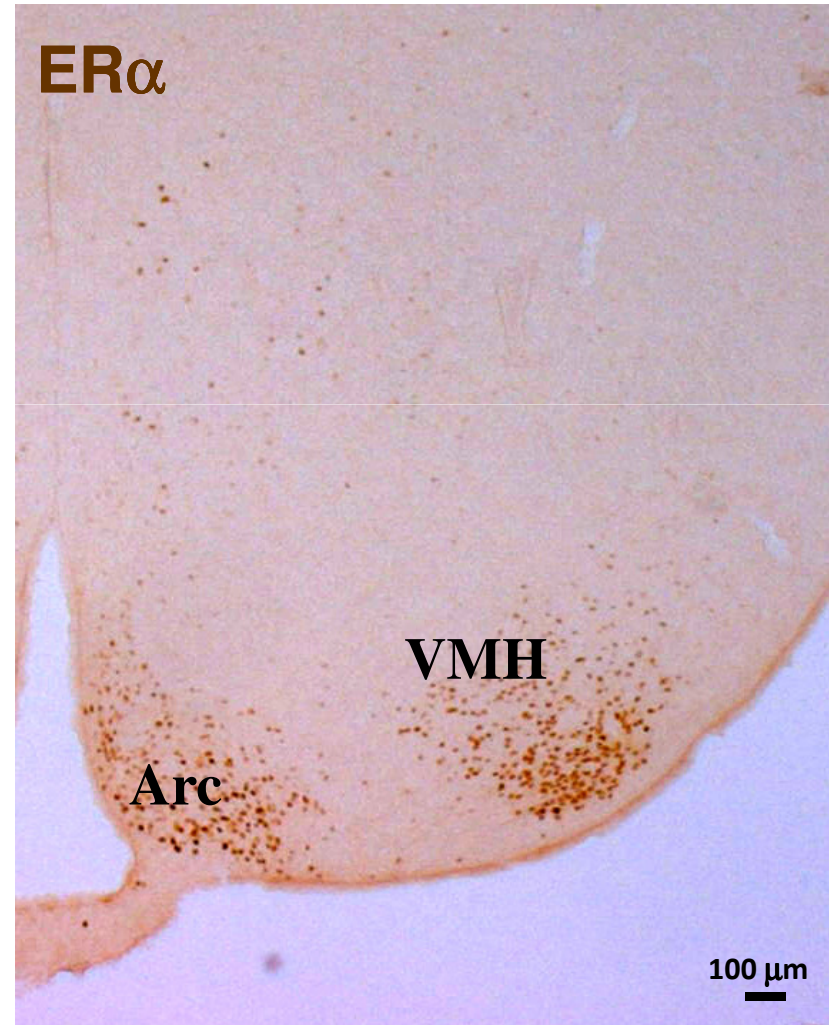
Estradiol regulates food intake



BDNF and estrogen receptor alpha (ER α) in the hypothalamus

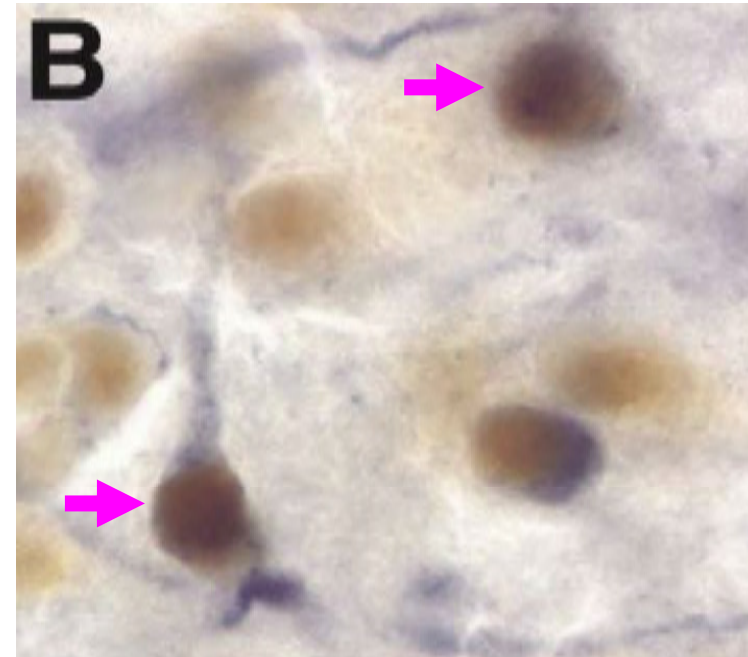
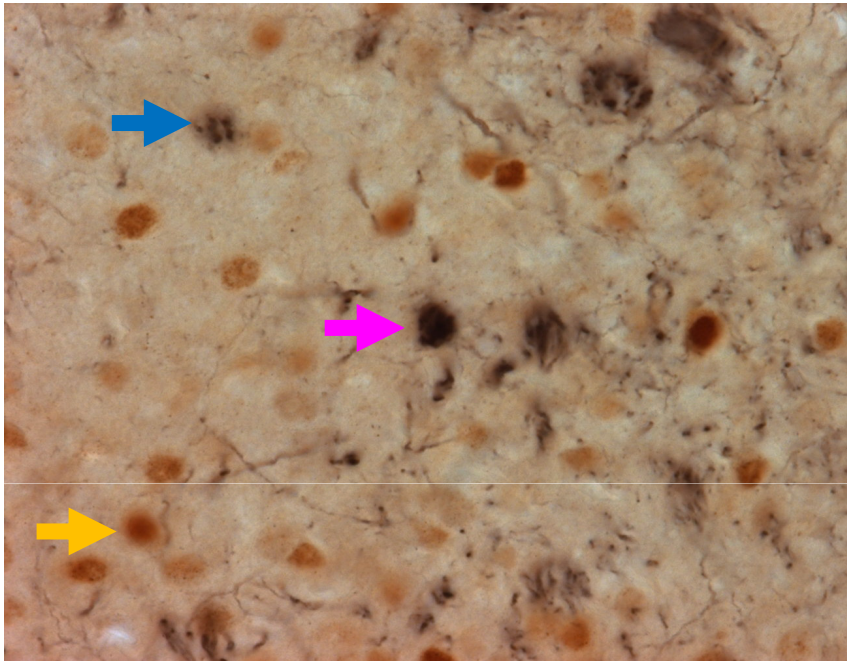





Xu, et al., Nat Neurosci 2003



Shi Lab

Colocalization of ER α and BDNF in the VMH

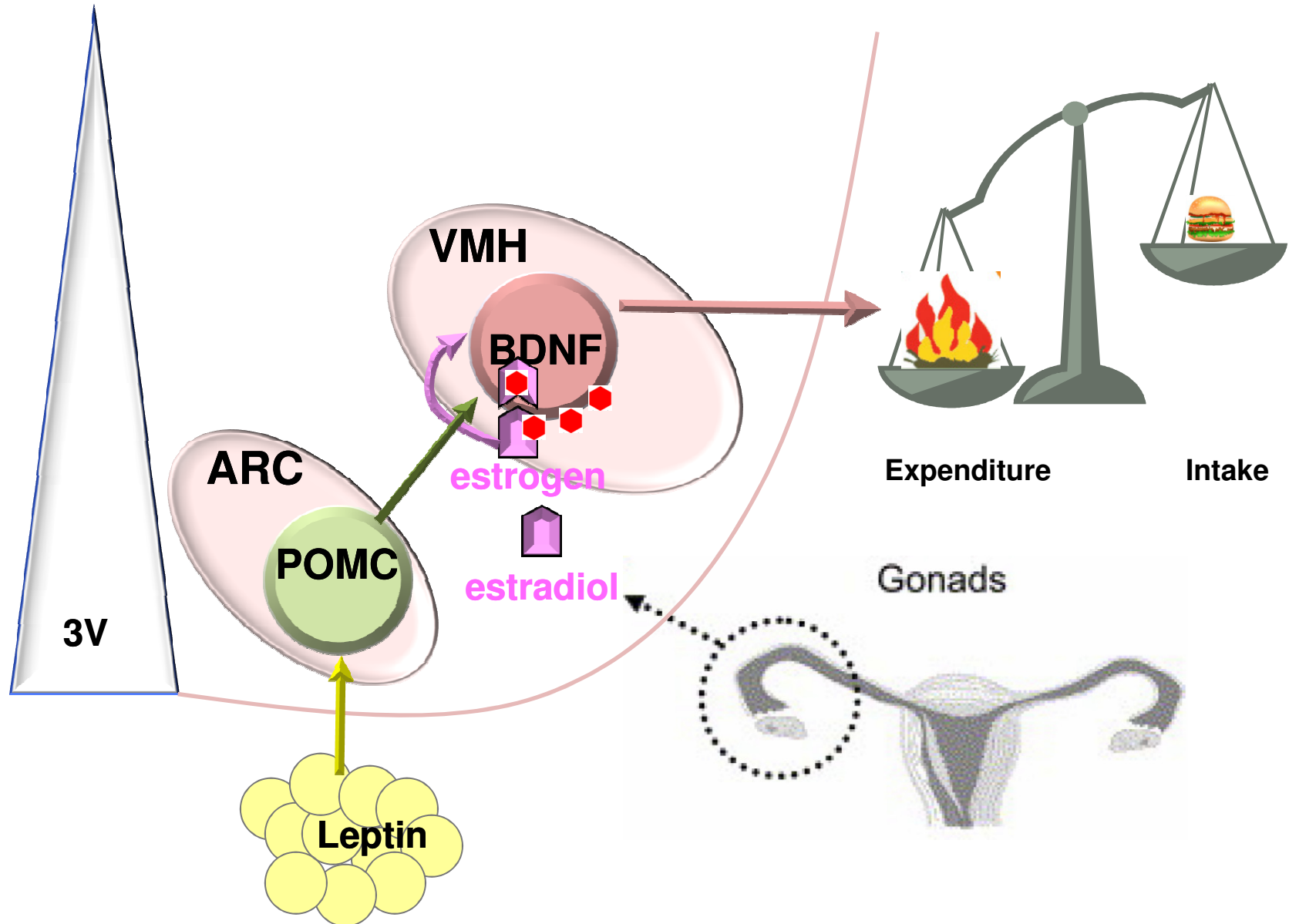


-  ER α : brown (DAB)
 -  BDNF: blue black (nickel-enhanced DAB)
 -  BDNF + ER α
- Shi Lab

ER α : brown
BDNF: blue

Blurton-Jones, et al., J Comp Neurol 2004

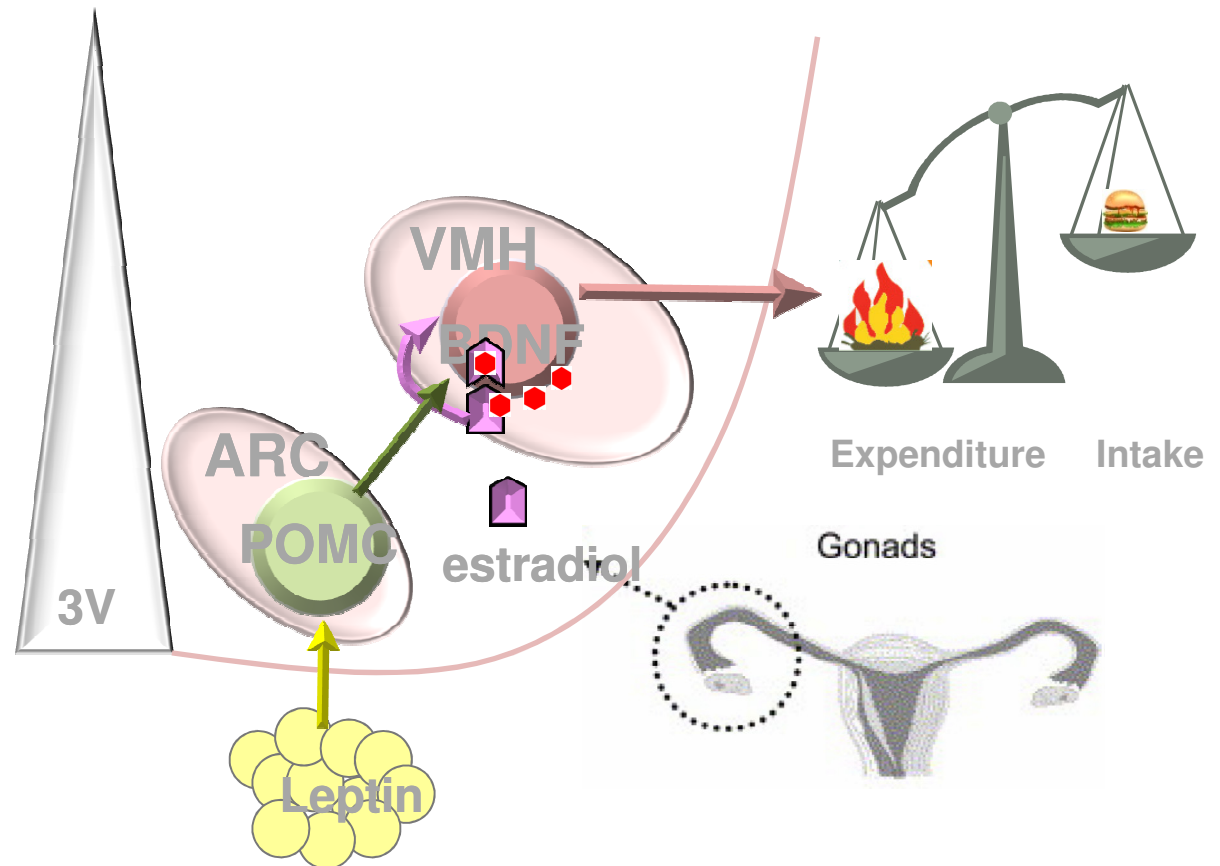
Potential regulation of BDNF by estradiol



Hypothesis: Central BDNF expression and action are regulated by estradiol.

Q1: Is central BDNF expression regulated by estradiol?

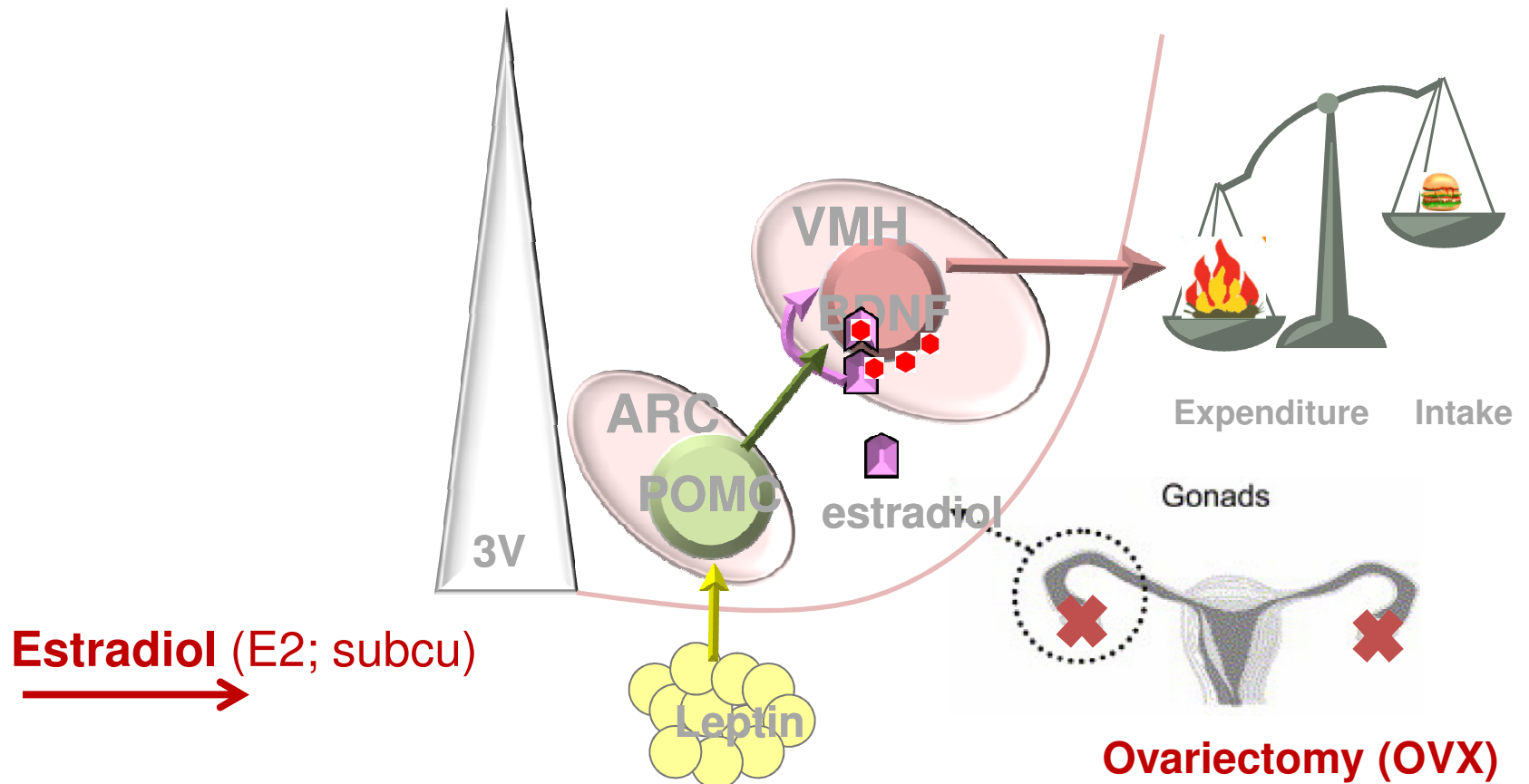
Q2: Is central BDNF action regulated by estradiol?



Hypothesis: Central BDNF expression and action are regulated by estradiol.

Q1: Is central BDNF expression regulated by estradiol?

Q2: Is central BDNF action regulated by estradiol?



Q1: Is central BDNF expression regulated by estradiol?

(1) Does ovariectomy (OVX) or estradiol (E2) replacement modulate VMH BDNF gene expression?

Experiment groups

Sham-Oil

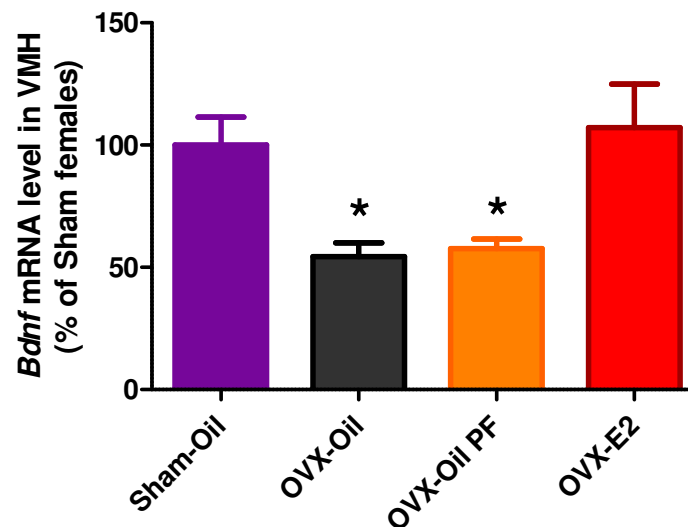
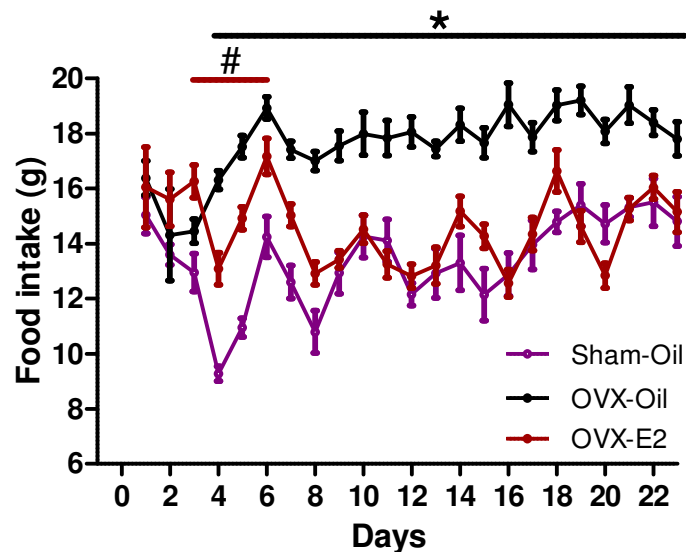
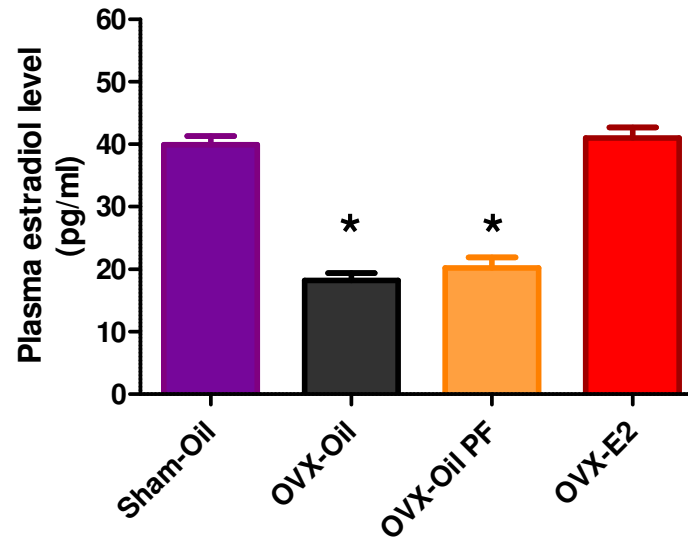
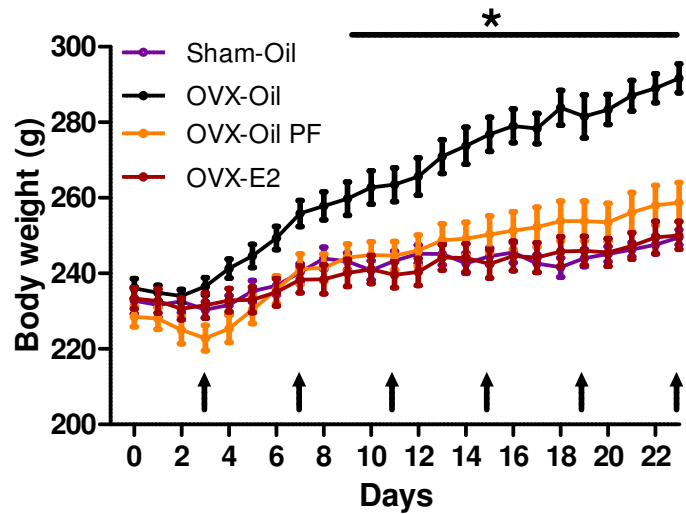
OVX-Oil ad lib

OVX-Oil pairfeed (PF) (pairfeed to Sham-Oil)

OVX-E2

Q1: Is central BDNF expression regulated by estradiol?

(1) Does ovariectomy (OVX) or estradiol (E2) replacement modulate VMH BDNF gene expression?

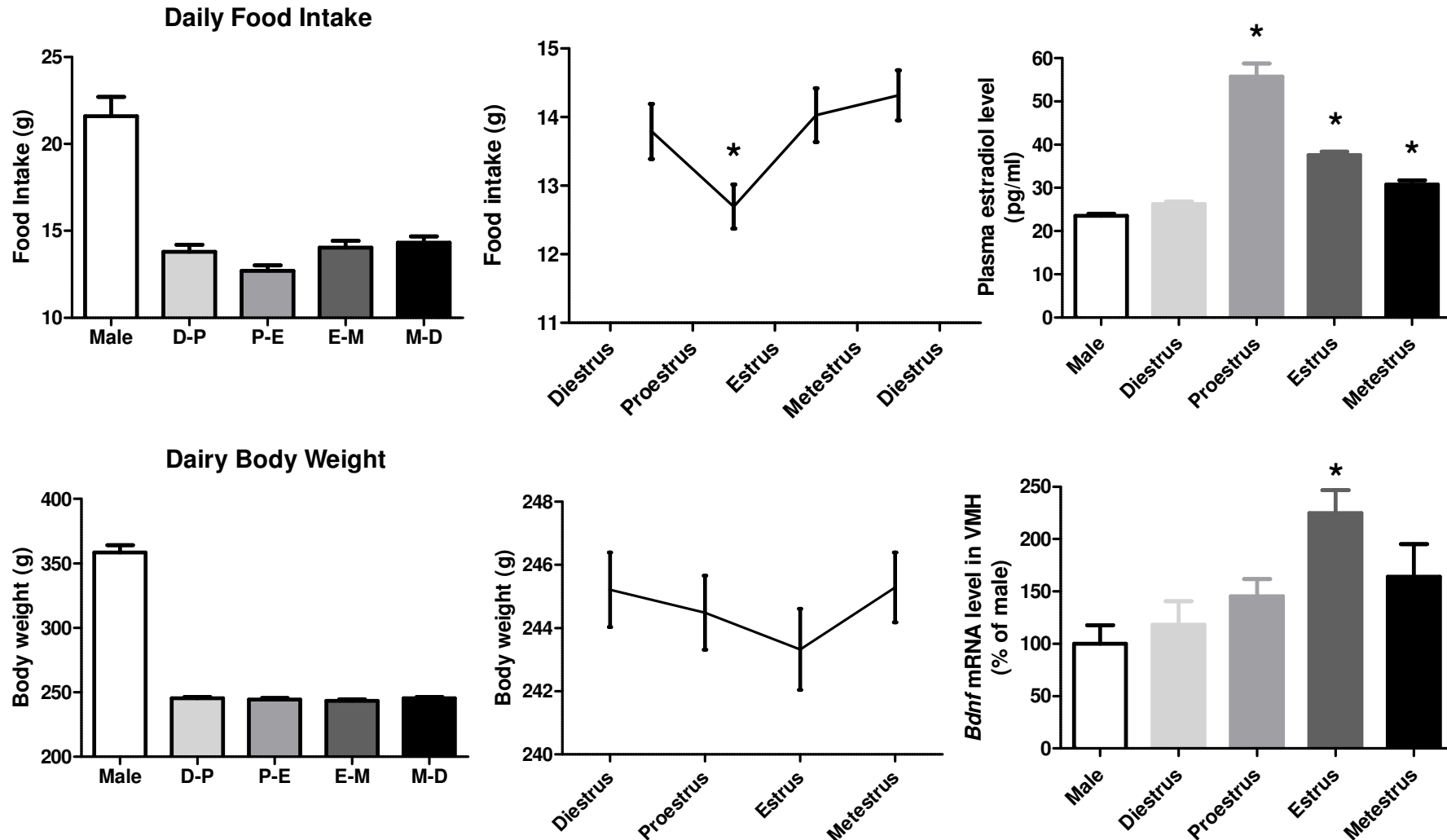


Q1: Is central BDNF expression regulated by estradiol?

(2) Do male and female rats have different BDNF expression?

Does estrous cycle modulate VMH BDNF gene expression?

Experiment groups (Ordered 10-week old male and female rats, sacrificed at 12-week of age)



Summary 1

Q1: Is central BDNF expression regulated by estradiol?

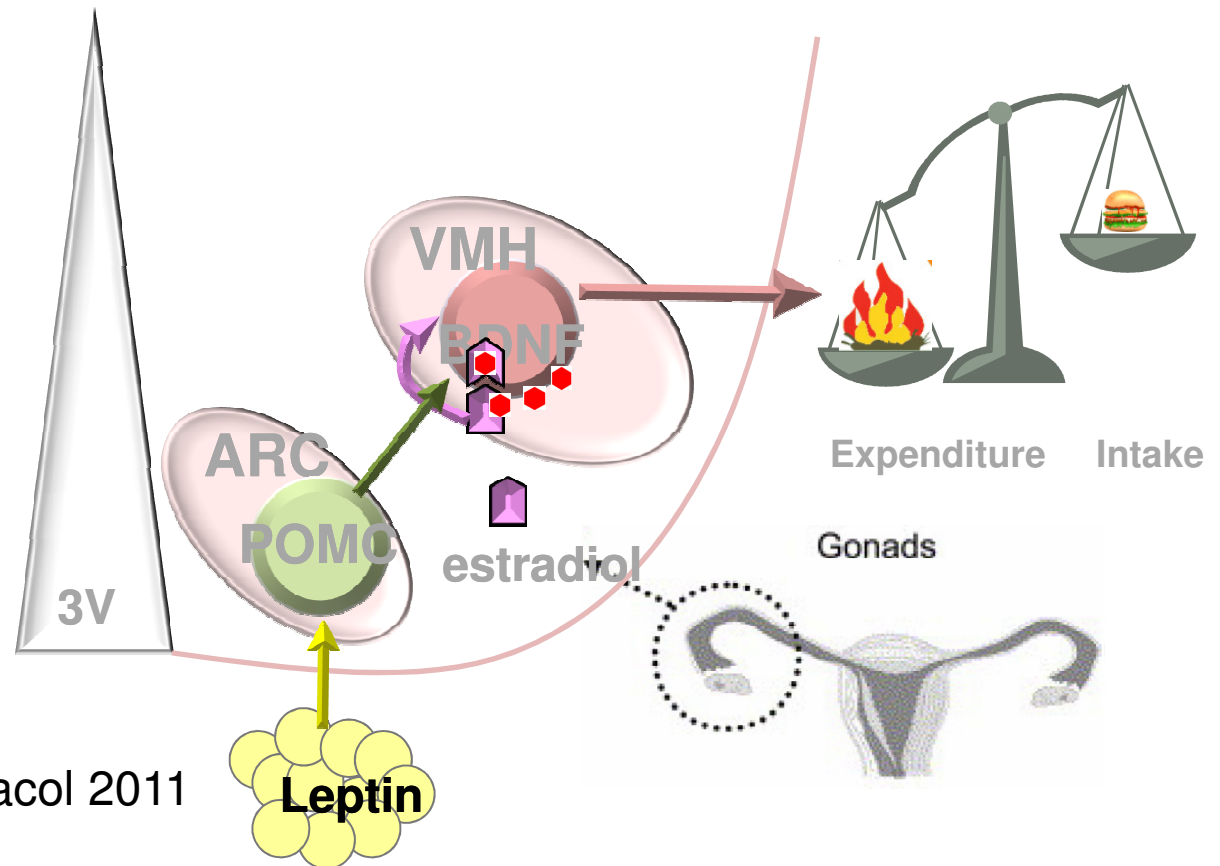
BDNF gene expression is regulated in an estradiol-sensitive manner.

- OVX decreases BDNF gene expression; reversed by estradiol replacement.
- Estrous female rats have greater BDNF expression than males.
- BDNF expression is dynamically regulated across estrous cycle with a temporal elevation at estrous phase.

Hypothesis: Central BDNF expression and action are regulated by estradiol.

Q1: Is central BDNF expression regulated by estradiol?

Q2: Is central BDNF action regulated by estradiol?



Clegg, et al., Diabetes 2006

de Souza, et al., Eur J Pharmacol 2011

Gao, et al., Nat Med 2007

Q2: Is central BDNF action regulated by estradiol?

(1) Is central BDNF's anorexic effect regulated by estradiol?

Experiment groups

Male-Oil

Sham-Oil

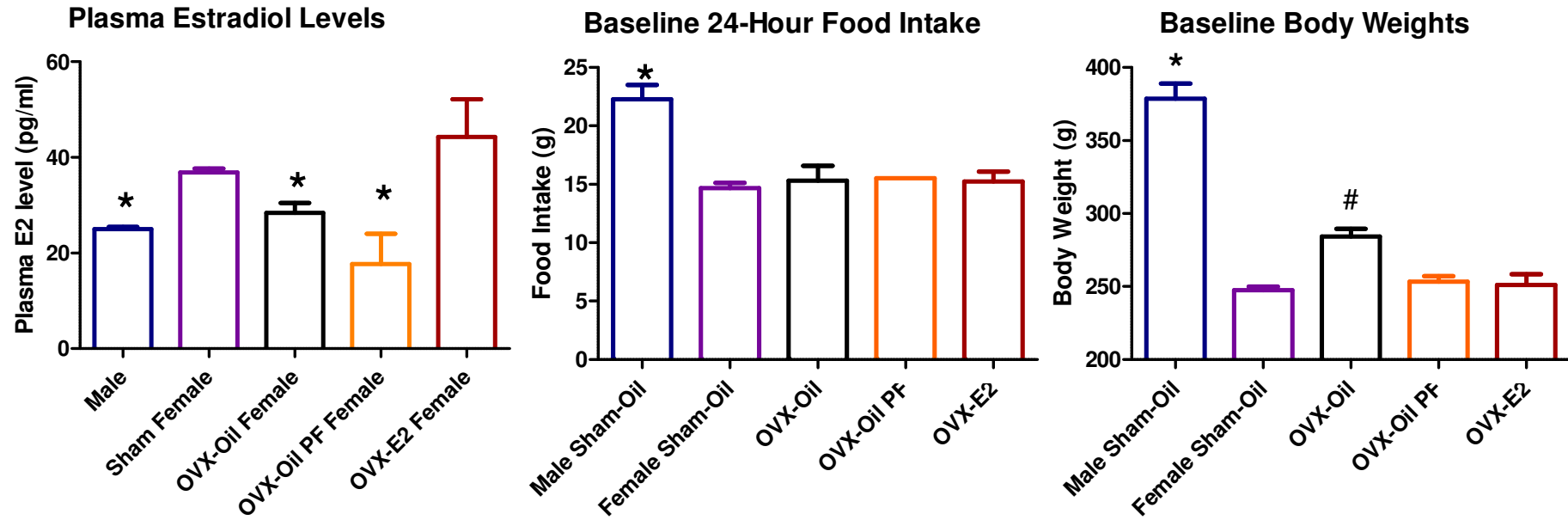
OVX-Oil ad lib

OVX-Oil pairfeed (PF) (pairfeed to Sham-Oil Female)

OVX-E2

Q2: Is central BDNF action regulated by estradiol?

(1) Is central BDNF's anorexic effect regulated by estradiol?



Experiment procedure

Light	Dark	Light
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**Lights
On**

**i3vt
0.1µg, 0.3µg
BDNF or
vehicle**

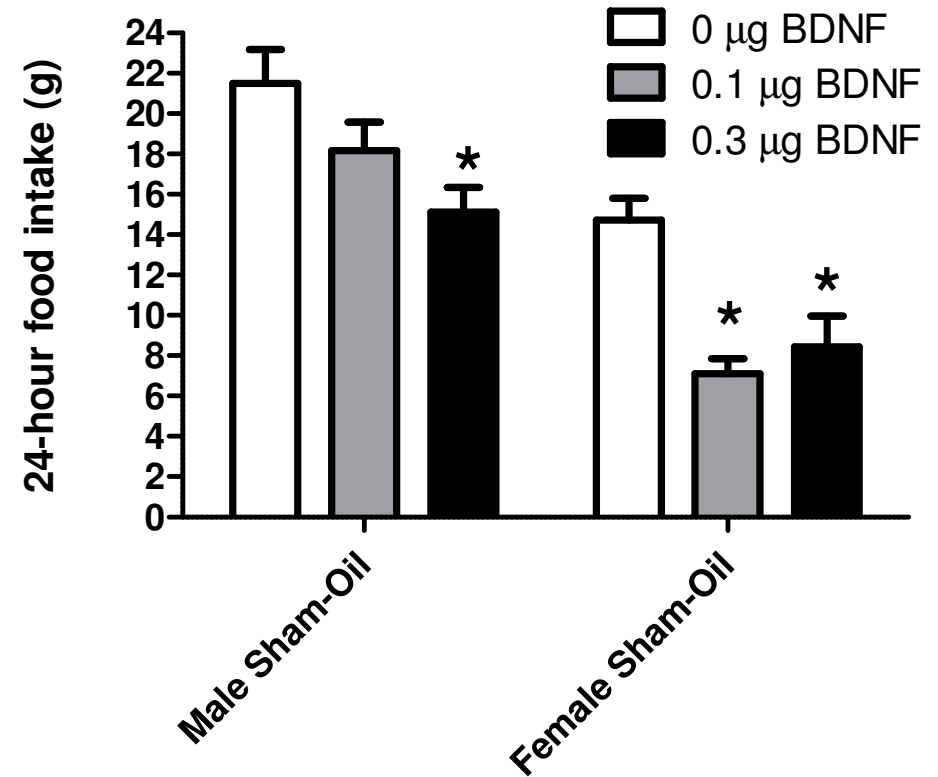
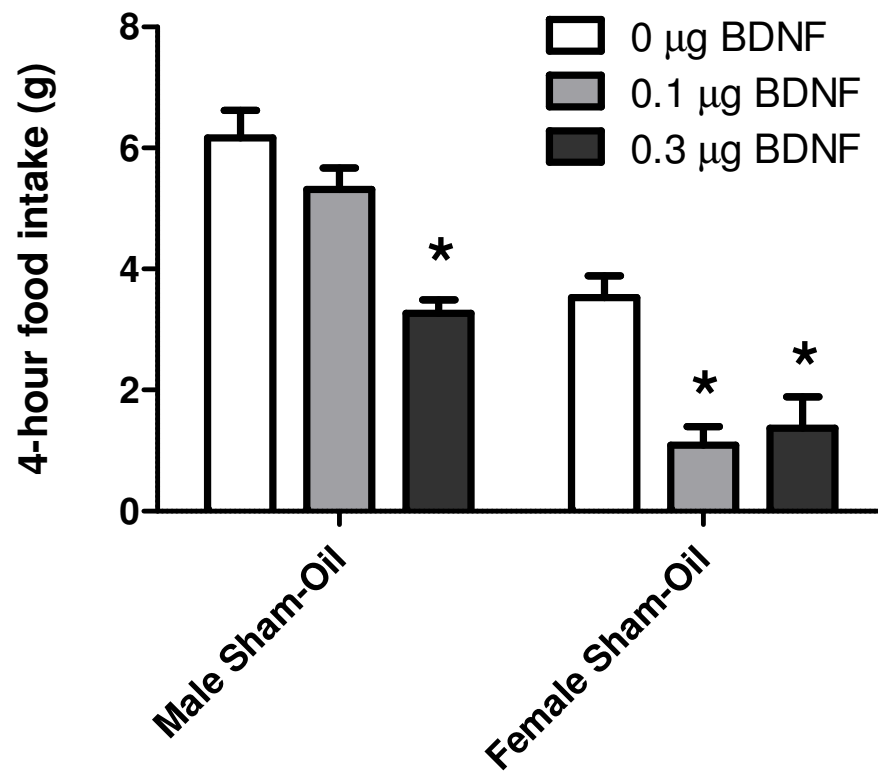
Lights out;

**4-hour
food intake**

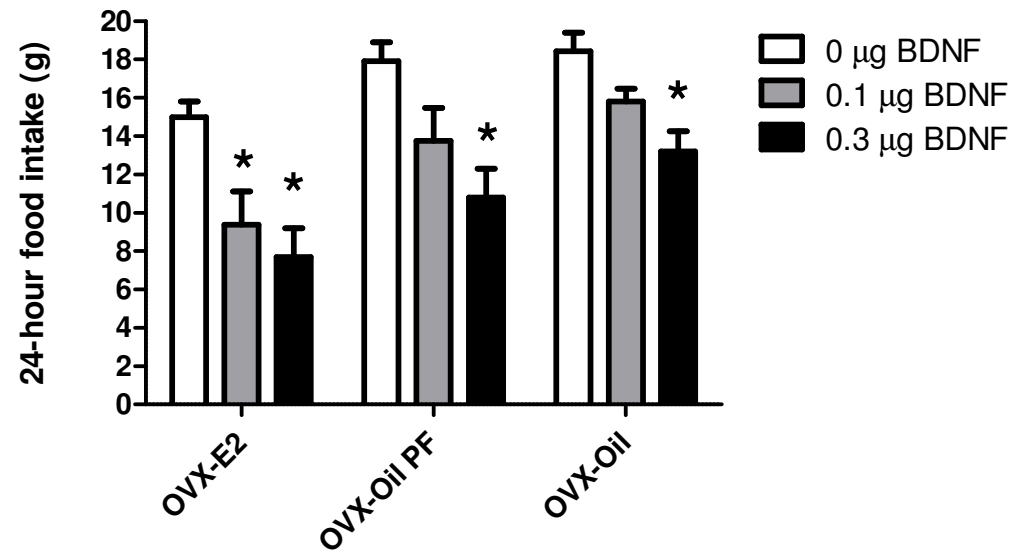
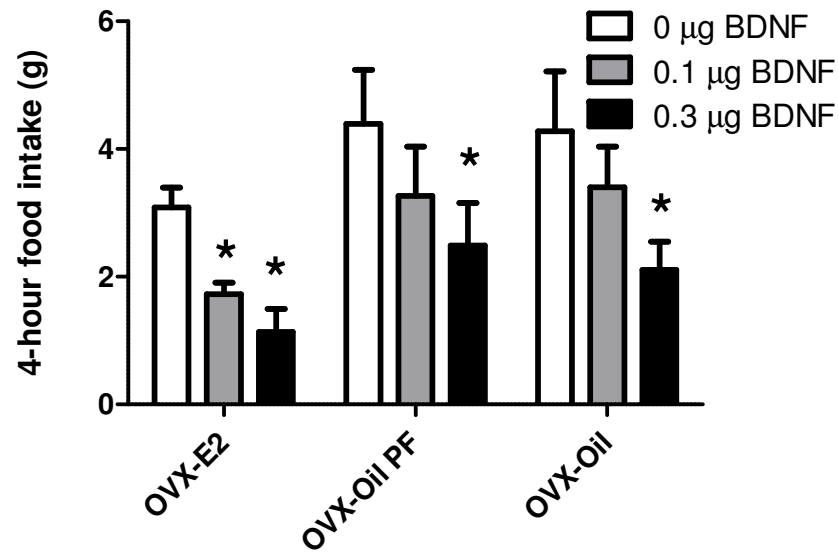
**24-hour
food intake**

Q2: Is central BDNF action regulated by estradiol?

(1) Is central BDNF's anorexic effect regulated by estradiol?



Q2: Is central BDNF action regulated by estradiol?
(2) Does ovariectomy or estradiol replacement regulate BDNF's anorexic effect?



Q2: Is central BDNF action regulated by estradiol?

(3) Is central BDNF's effect on energy expenditure different between males and females?

Experiment procedure



**Lights
On**

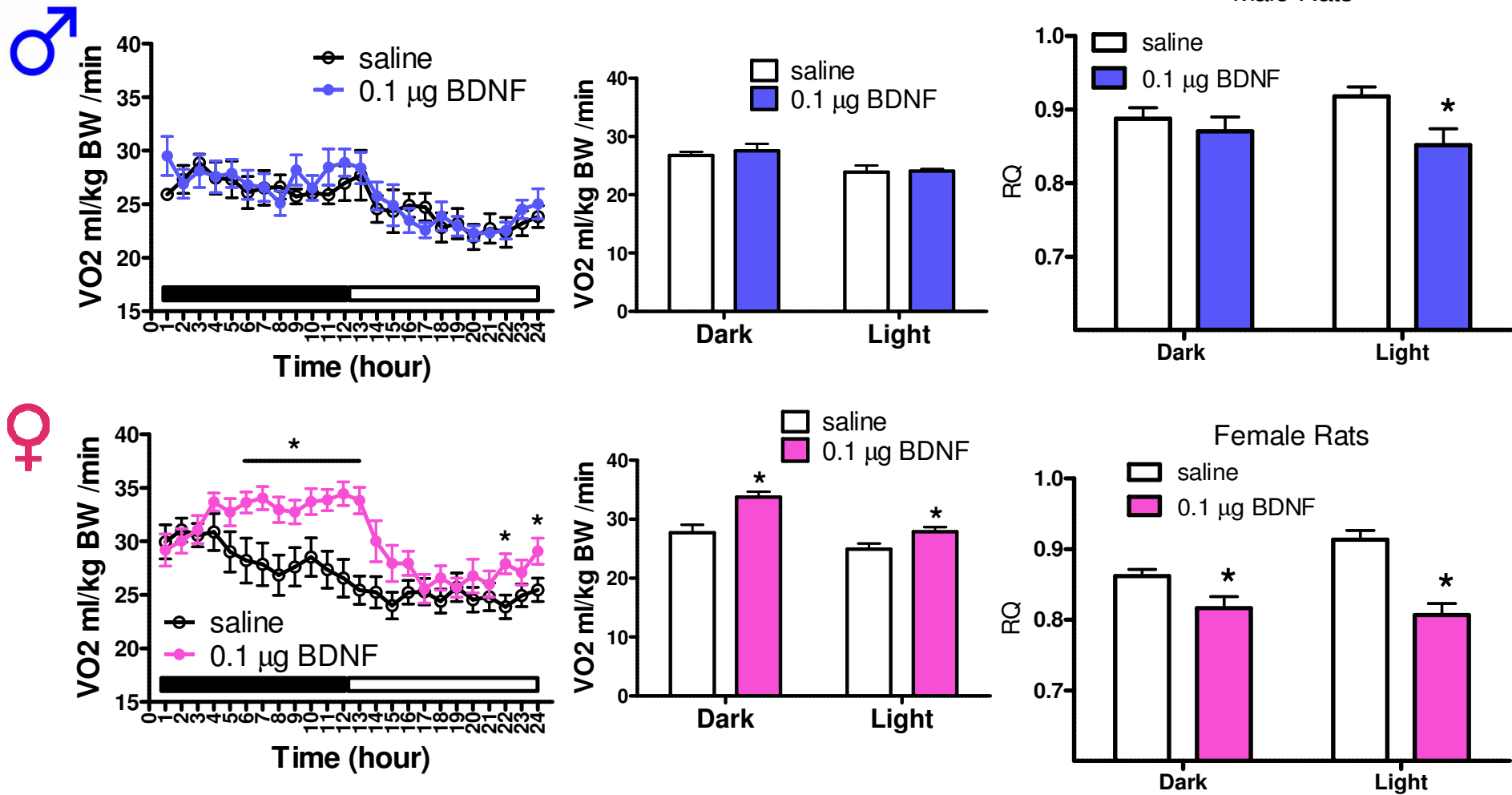
**i3vt
0.1µg
BDNF or
vehicle**

Lights out;

**24-hour
energy expenditure**

Q2: Is central BDNF action regulated by estradiol?

(3) Is central BDNF's effect on energy expenditure different between males and females?



Liu, Zhu, Shen, Shi. Unpublished.

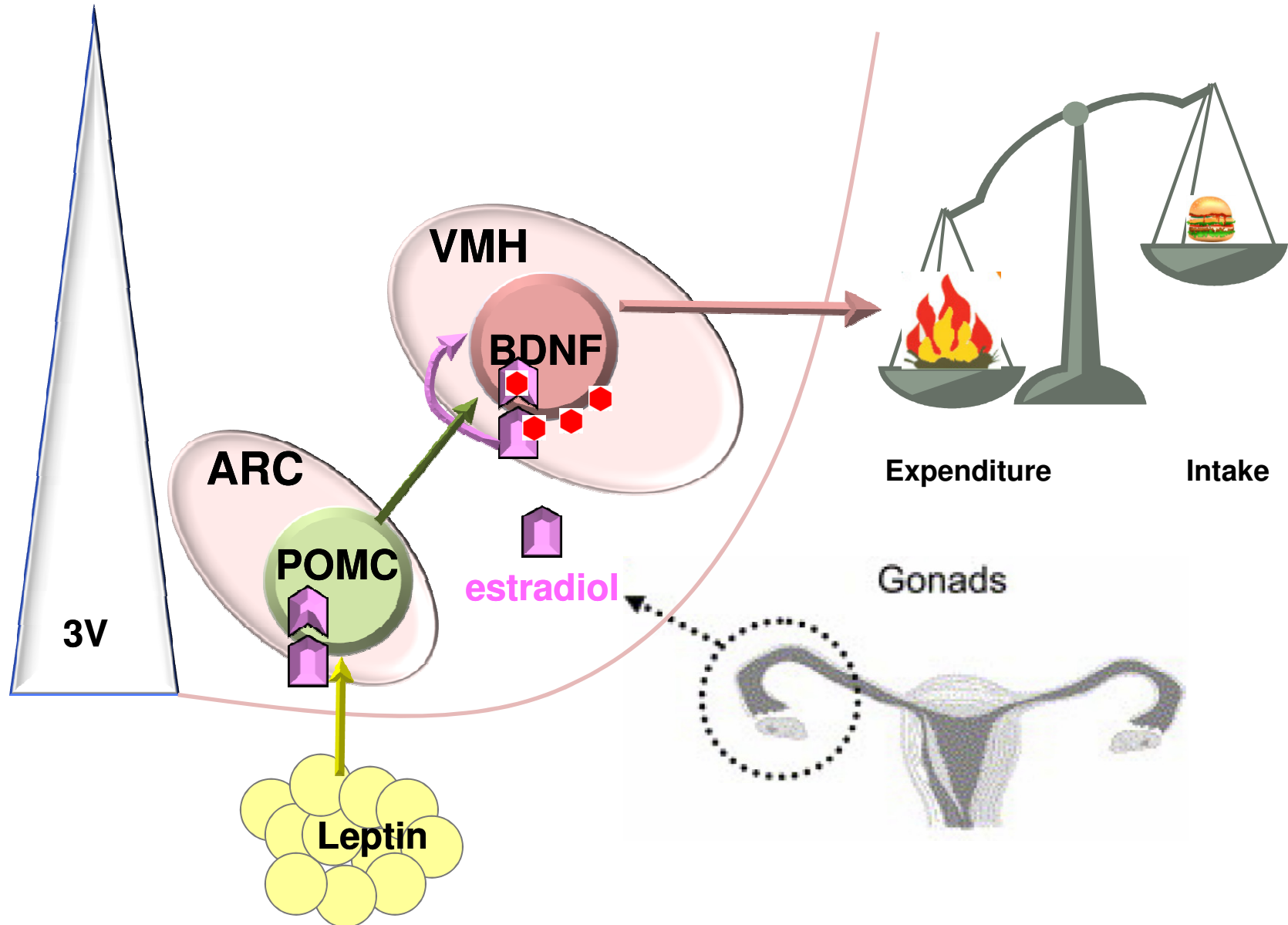
Summary 2

Q2: Is central BDNF's action regulated by estradiol?

- Estrous female rats respond to a lower dose of BDNF than male rats to reduce food intake.
- Estradiol-replaced OVX rats respond to a lower dose of BDNF than oil-injected OVX rats to reduce food intake.
- Central administration of a low dose (0.1 μg) of BDNF increased energy expenditure in female but not male rats.
- Central administration of a low dose (0.1 μg) of BDNF increased lipid oxidation during dark and light phases in females and only during light phase in males.

Conclusion

Estradiol increases BDNF central expression and action.



Acknowledgement



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**THE
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SOCIETY**

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