

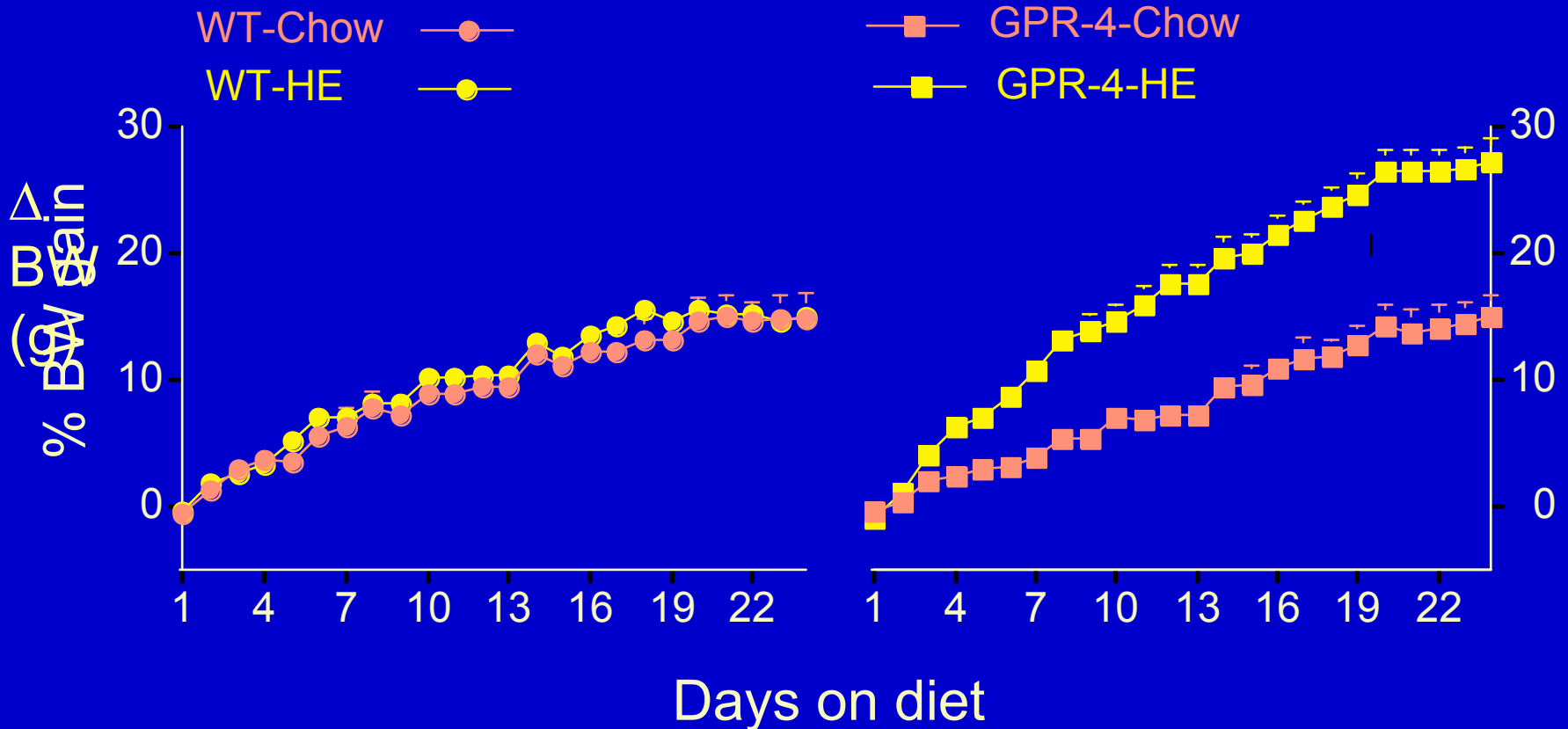
# Results from rats may also apply to peri- and post-menopausal women

- A change in body shape occurs, shifting energy stores from the periphery toward the center.
- “All my extra calories go to my middle” is a cri du cour at this time of life.
- Leanness is preserved with diet and exercise, but changes in shape still occur.
- Is this a consequence of decreased GnRH stimulation of POMC neurons?

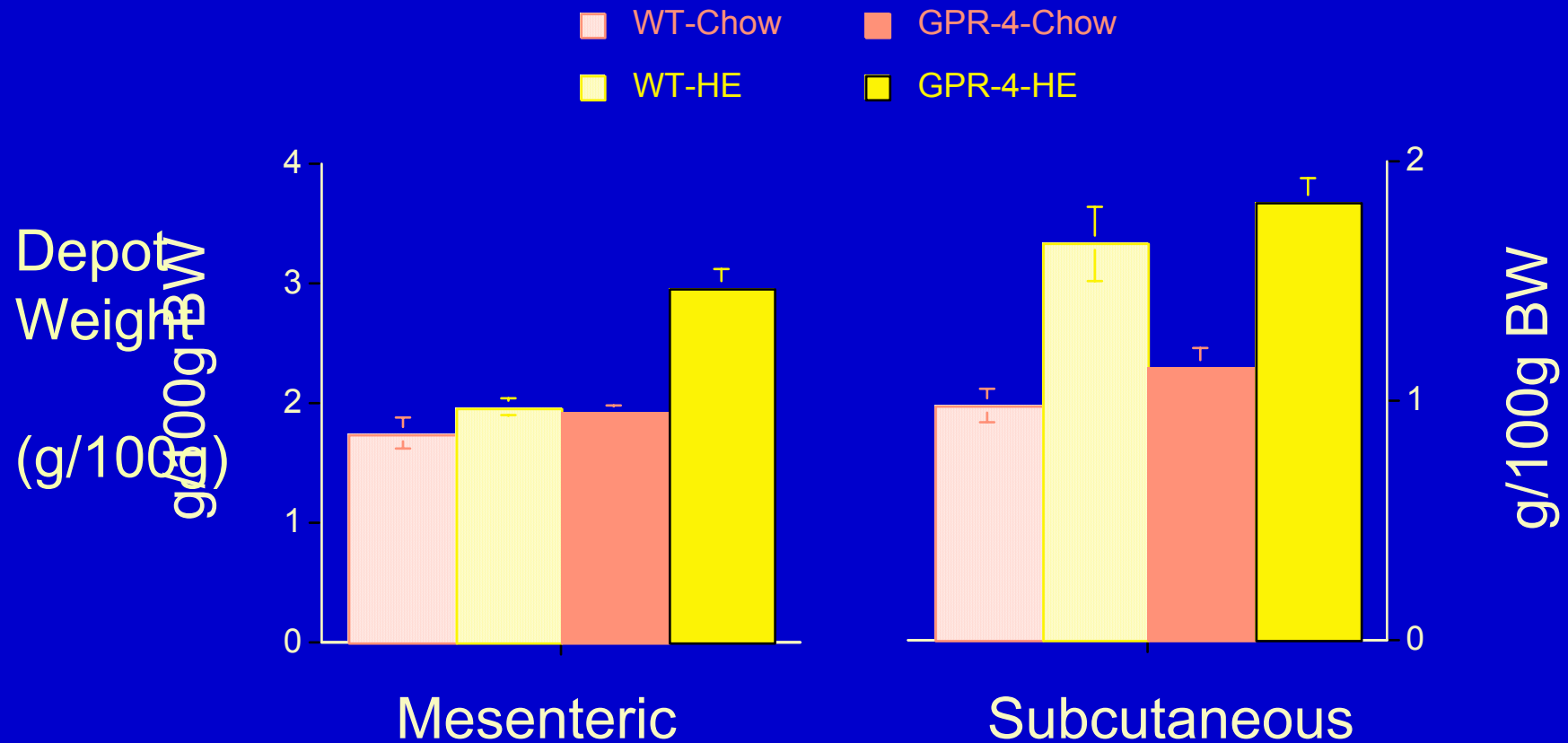
# Interaction between GnRH & Diet

- GPR-4 rats, made by RI Weiner, UCSF, express a transgene consisting of a GnRH promoter and coding region of phosphodiesterase-4.
- The transgenic female rats have blunted GnRH responses to inputs mediated by cAMP *in vitro* and diminished LH *in vivo*, have polycystic ovaries and early anovulation (100% anovulatory at 9 months of age).
- *Studies were done by Gomez, laFleur, Weiner, Dallman and El Majdoubi, UCSF. Rats were 3 months old.*

# High Energy Diet increases BW (through increased caloric intake) only in GPR-4 Females



# High Energy Diet results in Abdominal Obesity only in GPR-4 Females



# High Energy Diet and low GnRH responsiveness result in Abdominal Obesity in Female Rats

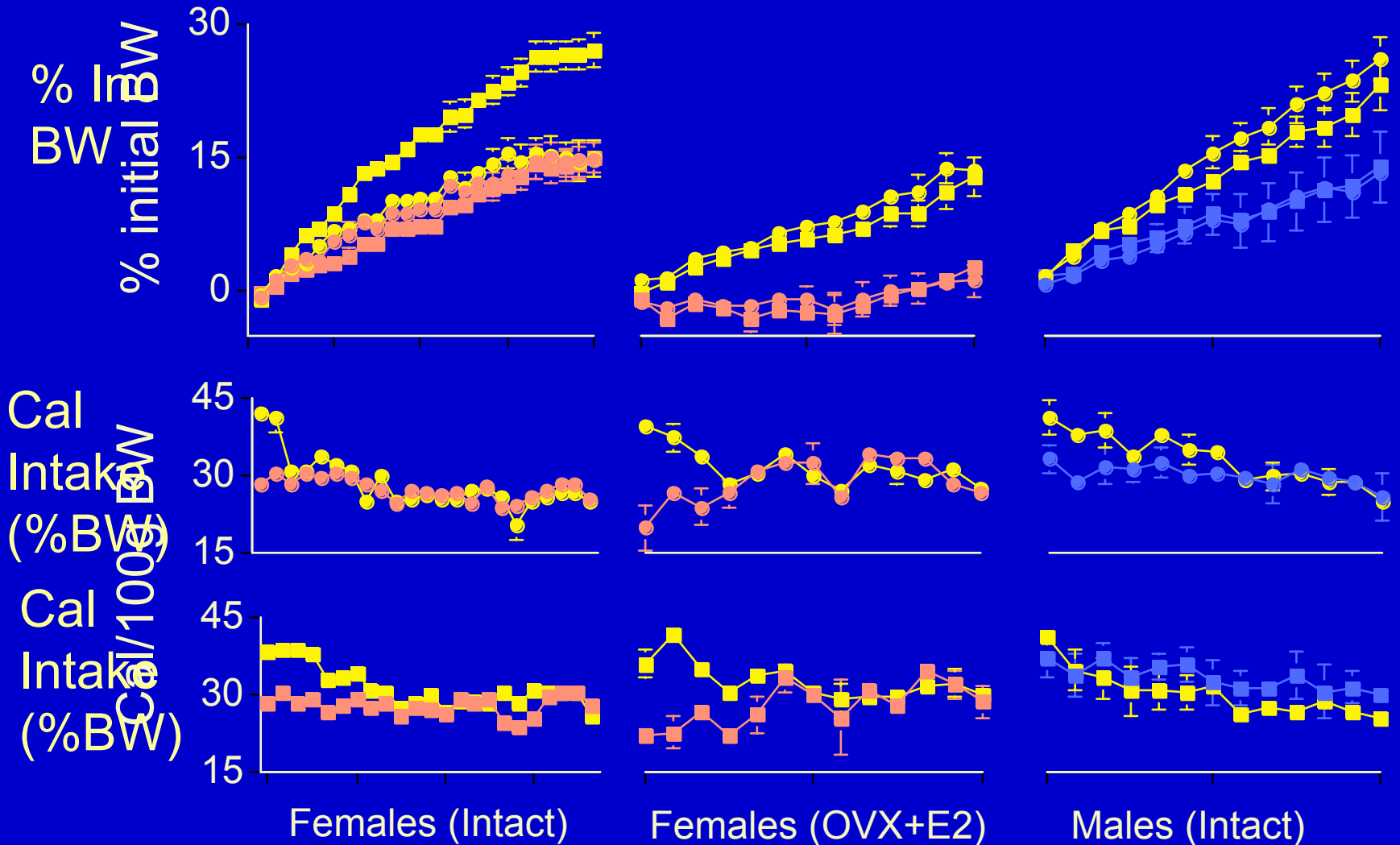
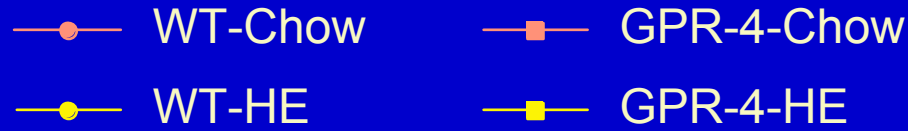
- Increased caloric intake explains abdominal obesity in female GPR-4 rats, compared to wild type.
- Changes in circulating hormones do not explain differences between WT and GPR-4 females.
- With OVX + estradiol Rx, both WT and GPR-4 females gain BW & become abdominally obese on HE diet.
- Both WT and GPR-4 males gain weight & become abdominally obese on HE diet.
- Horvath and his lab have shown GnRH axonal endings in interstitial space near POMC neurons (light & EM).

## We hypothesize that:

- In addition to the known negative effects of estradiol on energy balance, there may also be inhibitory GnRH regulation of food intake.
- Reduced GnRH secretion in GPR-4 females and in OVX Estradiol treated females reduces the stimulatory GnRH input to POMC cells in the hypothalamic ARCUATE nuclei.
- POMC (via  $\alpha$ -MSH) stimulates CRF neurons in PVN to cause decreased food intake.



# GPR-4 females overeat and gain weight on High Energy Diet





# OVX high E2 causes both WT and TG females To become abdominally obese on HE diet

