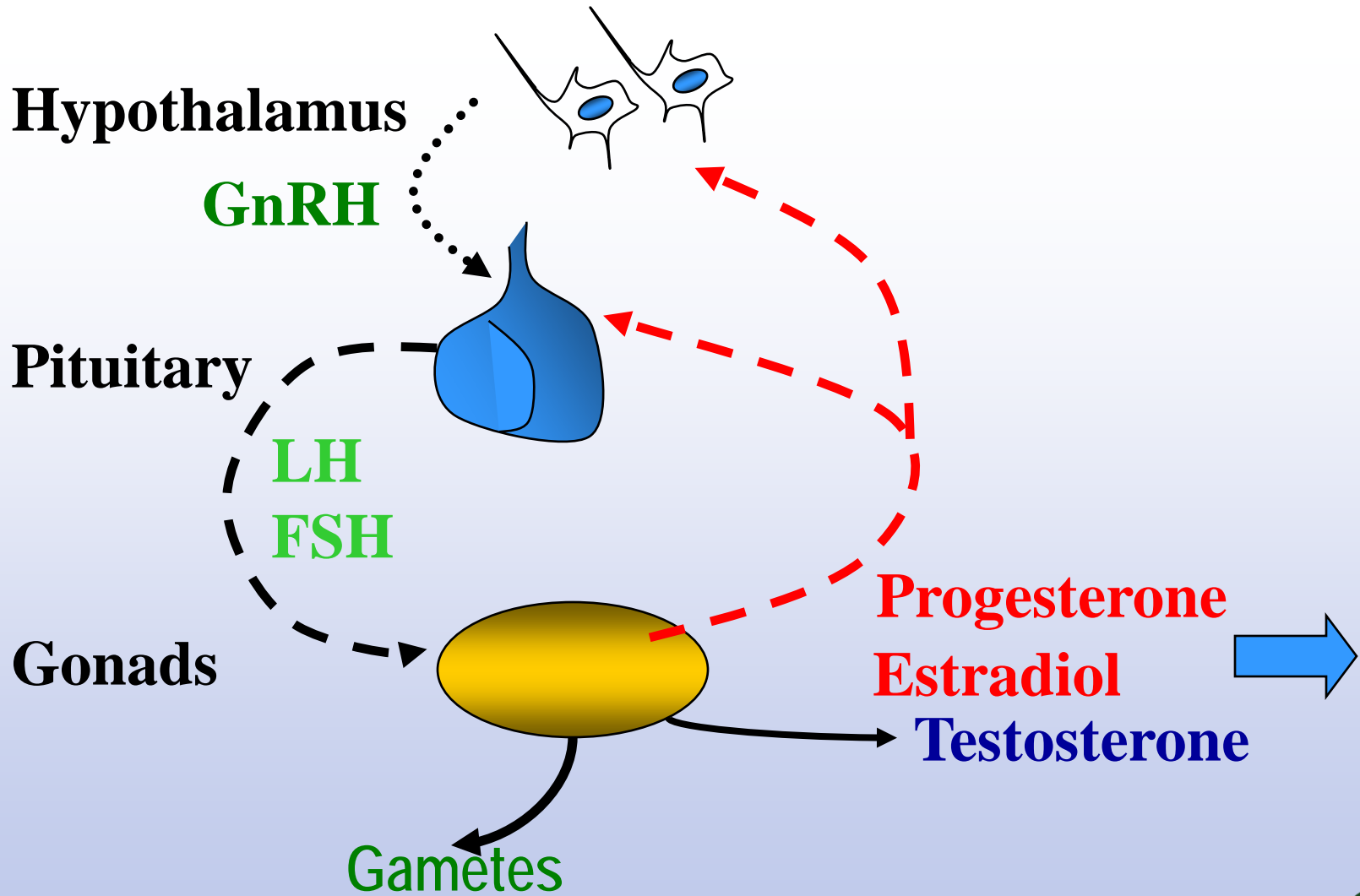


# Endocrine Activity

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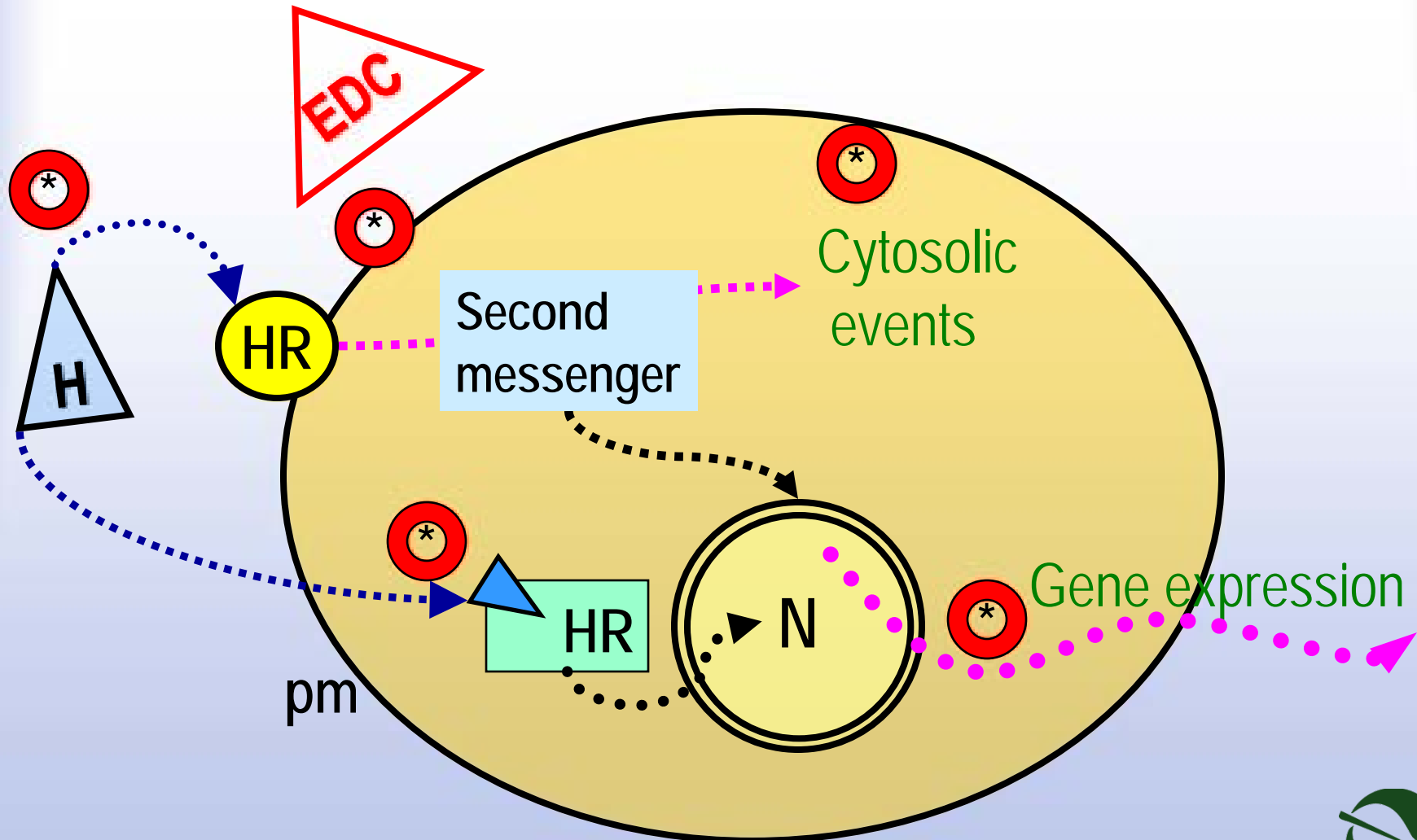
# The Endocrine System in Reproduction



- There is evidence that BPA is an endocrine disrupting chemical (EDC).
- OEHHA identified 35 original articles that address one or more of the proposed mechanism of action of an BPA.



# Endocrine Activity: Mechanism / Disruption



# 1. Interaction of BPA with estrogen receptor:

- Eleven *in vitro* studies.

Number of studies	Estrogen receptor	Model	EC <sub>50</sub> (μM)
8	Human	Various cell lines (reporter gene)	0.01 to 50
3	Rat	Anterior pituitary (PRL secretion); HepG2 cells (reporter gene)	0.02 to 0.63



## 2. Interaction of BPA with androgen receptor (AR):

- Three *in vitro* studies.

### Model:

Two cell lines cotransfected with the human AR and a reporter gene.

### Result:

BPA inhibit AR activity ( $IC_{50} = 1 \mu\text{M}$  to  $7 \mu\text{M}$ ).



### 3. Effects of BPA on sex hormone binding proteins:

- Three studies.

Model	Competition	IC <sub>50</sub>
Human SHBG	<0.01% for DHT	-
Human SHBG	Testosterone Estradiol	51 µM 13.6 µM
Rat AFP	0% for Estradiol	-



## 4. Effects of BPA on estrogen receptor- $\alpha$ expression:

### Model: Four *in vivo* studies

- Three studies used oral dose for various times.
- One study use a s.c. injection.

### Results:

- $\uparrow$ ♀  $\downarrow$ ♂ (medium and high doses).
- Various effects in different hypothalamic nuclei:  
no effect, decrease, or increase in the ER expression.



## 5. Effects of BPA on progesterone receptor (PR) expression:

### Model:

- Two *in vivo* studies, (SD and Wistar rat);
- Oral dose 0.02 - 800 mg/kg-d x 3 days.

### Results:

- Increase in PR gene expression in both studies.
  - In one of the studies BPA ↓ the E<sub>2</sub>-stimulated PR gene expression.



## 6. Effects of BPA on steroid production.

Model	Treatment	Results
pig granulosa cells	0.01 - 100 $\mu\text{M}$ /72 h	P: $\uparrow$ (low dose); $\downarrow$ (high dose) $\downarrow$ FSH-stimulated $\text{E}_2$ production
human granulosa cell line	20 - 100 $\mu\text{M}$ /48 h	$\downarrow$ FSH-stimulated $\text{E}_2$ production and aromatase expression
SD theca cells	0.01 - 1 $\mu\text{M}$ /48 h	$\uparrow$ P production
SD granulosa	0.02 and 0.1 $\mu\text{M}$	No effect



## 7. Effects of BPA on aromatase activity

### Model:

- Three *in vitro* studies
- Treatment: 10 -1000  $\mu\text{M}$ .

- human cell line
- human placenta microsomes
- equine purified enzyme

### Results:

- Decrease aromatase activity in the three studies.



## 8. Other endocrine related BPA effects:

- Alter enzymes and transporter proteins involved in E<sub>2</sub> metabolism.
- Reduce mean concentration, and pulse amplitude and frequency of luteinizing hormone in treated lambs.
- Increase production of prolactin in F344 rats but not on SD rats.
- Decrease glucose and Increase insulin production in mice (associated to ER).
- Increase insulin production in mice and mice pancreatic  $\beta$ -cells (associated to a plasma membrane and independent of ER  $\alpha$ ).
- Antagonize the thyroid hormone receptor from SD rat liver.
- Decrease thyroid hormone- induce activity in an amphibian bioassay.



# Summary of BPA endocrine effects:

- BPA binds and interact with estrogen receptor, androgen receptor, and sex hormone binding proteins.
- BPA modulates expression of estrogen and progesterone receptor.
- Increase P and decrease FSH-stimulated E<sub>2</sub> production.
- Decrease aromatase enzyme expression and alter enzymes and transporter proteins involved in E<sub>2</sub> metabolism.
- Reduce luteinizing hormone concentration.
- Increase production of prolactin.
- Decrease glucose and Increase insulin production in mice (dependent and independent to ER).
- Antagonize the thyroid hormone activity.

