

DOES INSULIN RESISTANCE CAUSE HYPERANDROGENEMIA OR HYPERANDROGENEMIA CAUSES INSULIN RESISTANCE IN PCOS

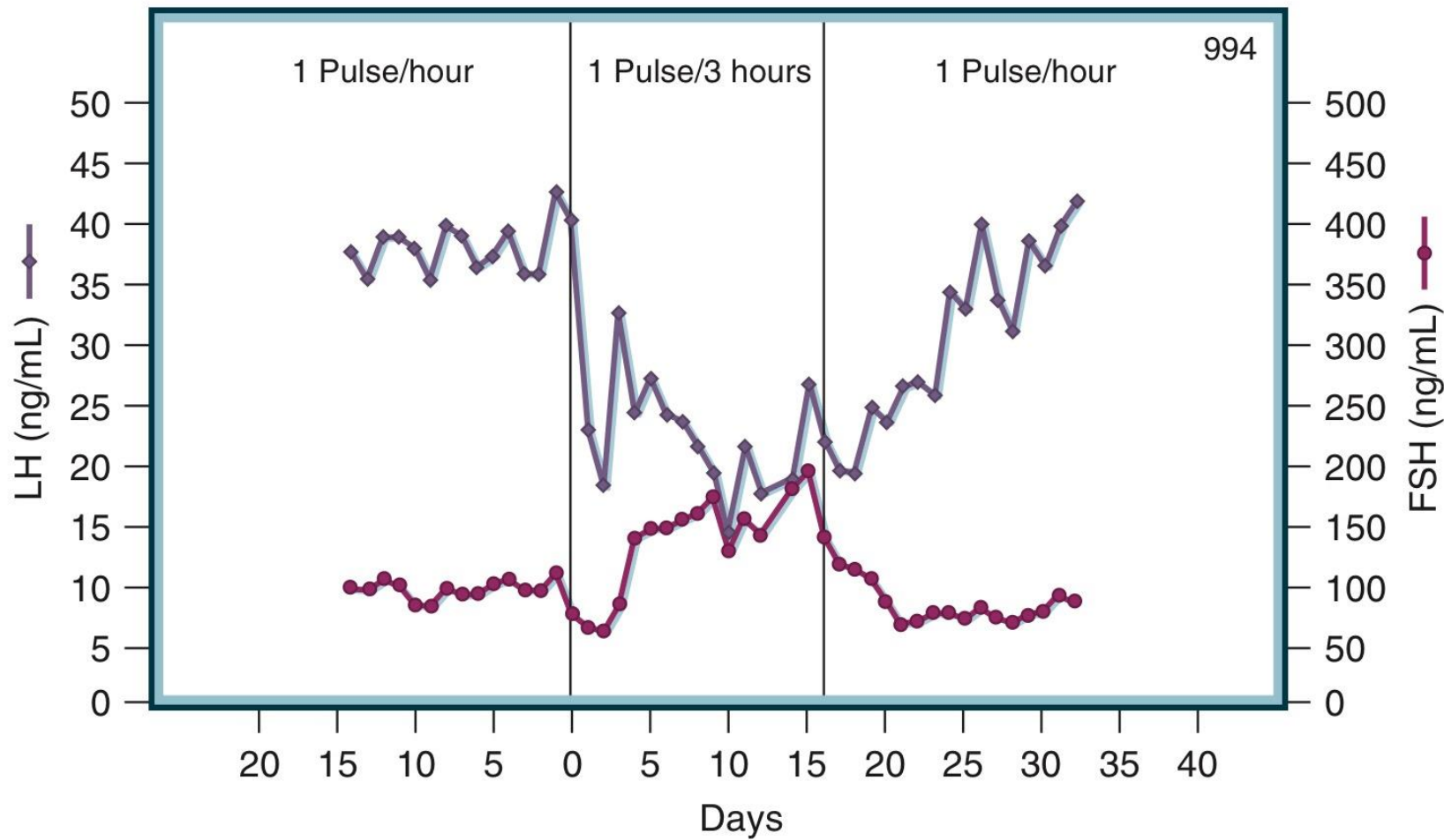
DR.GANAPATHI.B
DEPT.OF ENDOCRINOLOGY
ST.JOHNS MEDICAL COLLEGE
BANGALORE

INTRODUCTION

◆ In 18th century,- signs of androgen excess was coupled with metabolic abnormalities such as increased visceral fat

◆ 1921, Achard and Thiers reported the coexistence of diabetes mellitus with clinical signs of androgen excess in a postmenopausal woman—“Achard-Thiers syndrome” or “diabetes of the bearded women”

◆ Jean Vague introduced the term “android obesity” to define the abdominal fat accumulation



◆ Knobil's experiments-more rapid GnRH pulse frequencies favor luteinizing hormone (LH) secretion

PCOS

Characterized by –

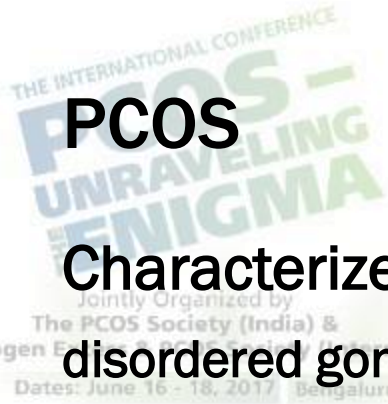
disordered gonadotropin secretion,

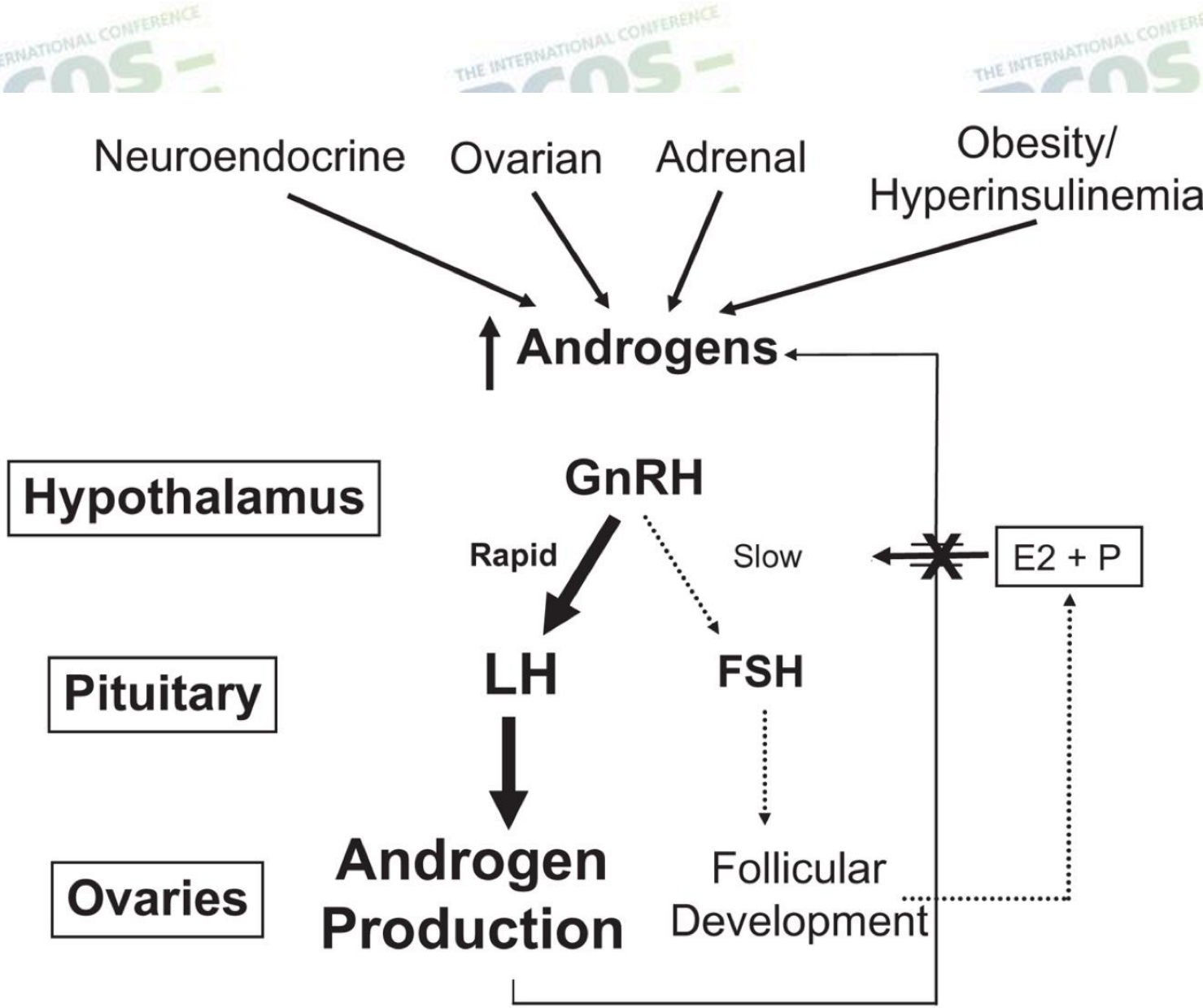
Hyperandrogenemia,

insulin resistance and hyperinsulinemia,

ovarian dysfunction, and

follicular arrest .





The
The Androgen E
Dates

The
The Androgen E
Dates

&
(International)
engaluru

&
(International)
engaluru

&
(International)
engaluru

DOES INSULIN RESISTANCE CAUSE HYPERANDROGENEMIA?

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

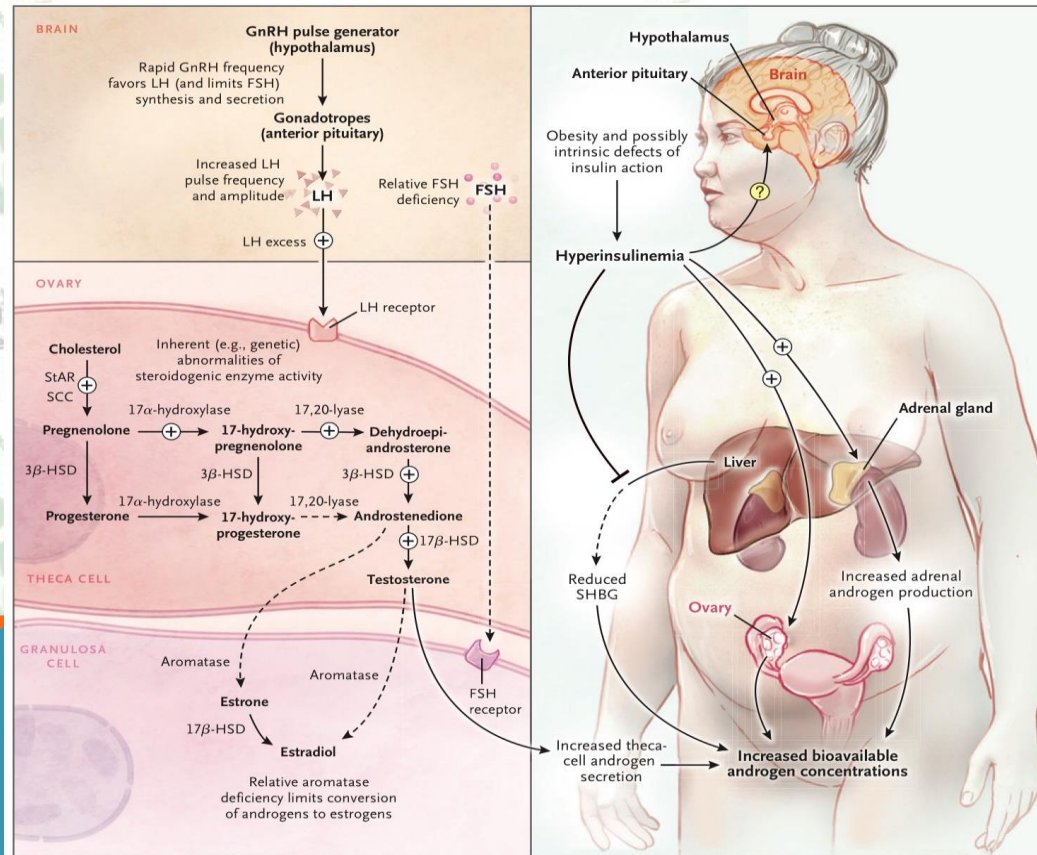
Dates: June 16 - 18, 2017 Bengaluru

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru



Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

INSULIN RESISTANCE CAUSES

- ◆ 1. Increase in GnRH release
- ◆ 2. Increase in Adrenal production of androgens
- ◆ 3. Reduction in SHBG production
- ◆ 4. Increase in Ovarian production of androgens

INSULIN AND DYSREGULATION OF HYPOTHALAMUS-HYPOPHYSIS-OVARY SIGNALLING

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

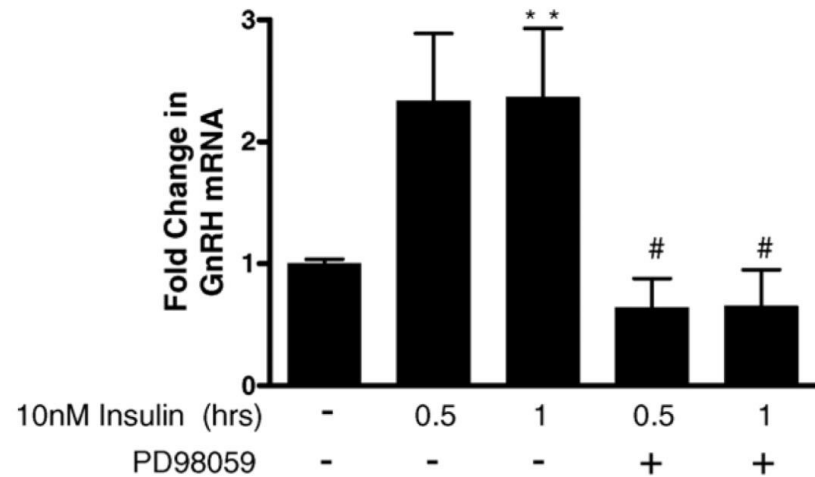
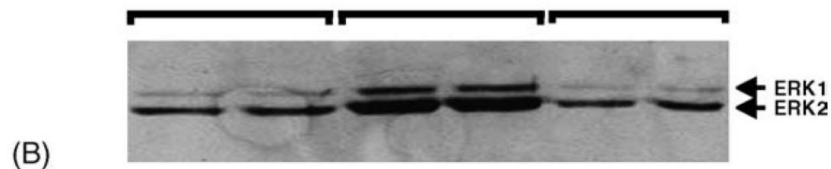
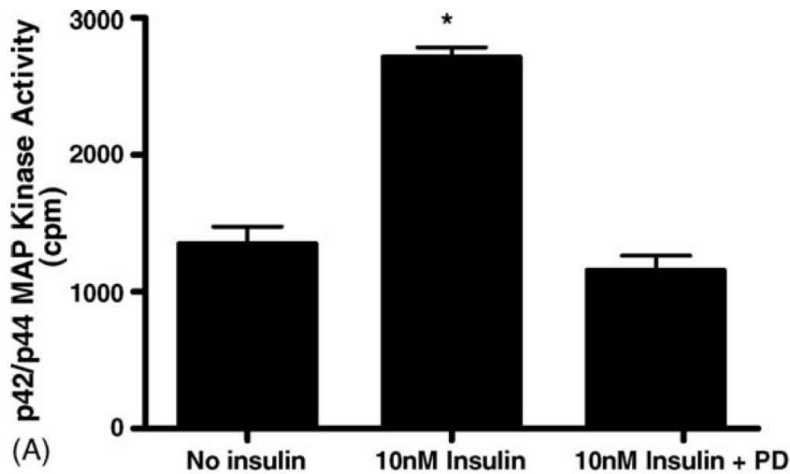
Dates: June 16 - 18, 2017 Bengaluru

Dates: June 16 - 18, 2017 Bengaluru

◆ Insulin increases GnRH gene transcription through the MAPK pathway

◆ As a result, increased GnRH synthesis and secretion lead to a subsequent elevation of LH levels

◆ LH stimulates ovarian theca cell androgen production



18, 2017 Bengaluru

Dates: June 16 - 18, 2017 Bengaluru

Insulin regulation of GnRH gene expression through MAP kinase signaling pathways, Molecular and Cellular Endocrinology, 2005

Dates: June 16 - 18, 2017 Bengaluru

The PCOS Society (India) & The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

INSULIN AND SEX HORMONE BINDING GLOBULIN

◆ Not per se by direct insulin action

◆ Via indirect mediators- glucose and fructose

◆ Monosaccharides down regulates hepatocyte nuclear factor 4-alpha (HNF-4alpha) activity

◆ Insulin represses insulin-like growth factor-1 binding protein (IGFBP-1) synthesis in a direct, rapid, and complete way in both the liver and the ovaries

◆ This allows for greater IGF-1 availability at ovaries and liver

INSULIN AND DYSREGULATION OF HYPOTHALAMUS-HYPOPHYSIS- ADRENAL SIGNALLING

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

- ◆ Insulin inhibits hippocampal activity
- ◆ indirectly enhances hypothalamic CRH secretion
- ◆ It has a possible direct role in both the hypothalamus and the hypophysis
- ◆ Insulin appears to augment adrenal cortex sensitivity to ACTH stimulation, with increased androgen secretion

THE INTERNATIONAL CONFERENCE
PCOS - UNRAVELING THE ENIGMA

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

THE INTERNATIONAL CONFERENCE
PCOS - UNRAVELING THE ENIGMA

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

THE INTERNATIONAL CONFERENCE
PCOS - UNRAVELING THE ENIGMA

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

THE INTERNATIONAL CONFERENCE
PCOS - UNRAVELING THE ENIGMA

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

THE INTERNATIONAL CONFERENCE
PCOS - UNRAVELING THE ENIGMA

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

THE INTERNATIONAL CONFERENCE
PCOS - UNRAVELING THE ENIGMA

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

SELECTIVE INSULIN RESISTANCE

THE INTERNATIONAL CONFERENCE
PCOS - UNRAVELING THE ENIGMA

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

THE INTERNATIONAL CONFERENCE
PCOS - UNRAVELING THE ENIGMA

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

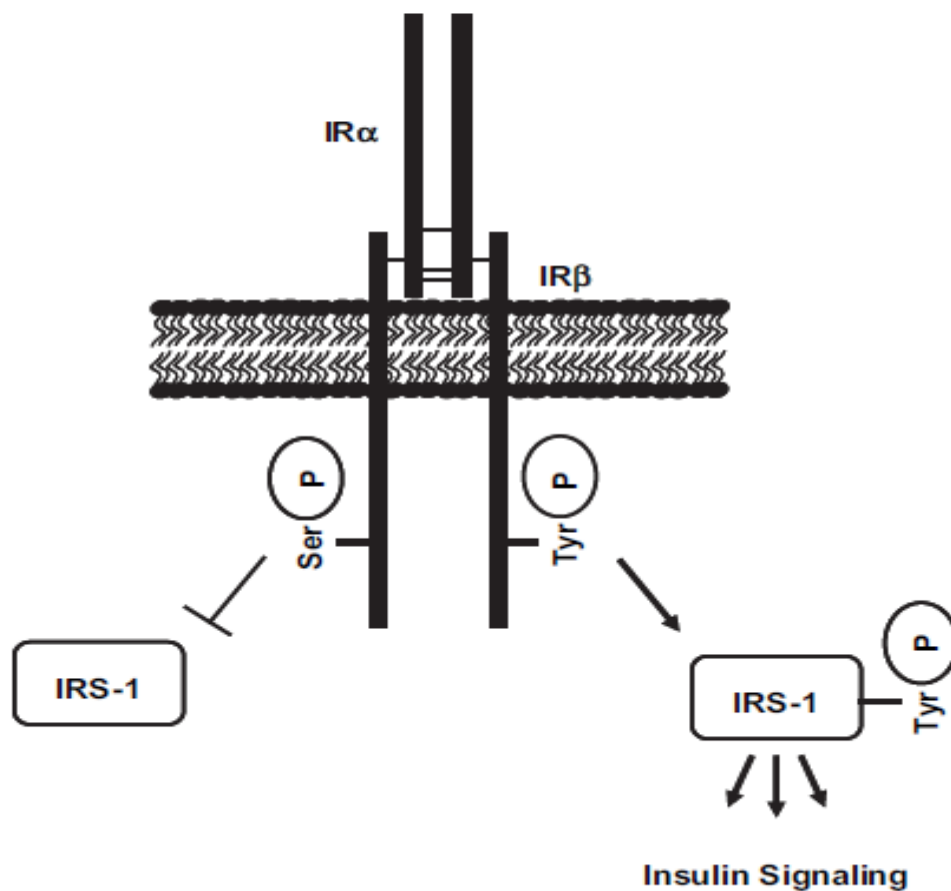
Dates: June 16 - 18, 2017 Bengaluru

THE INTERNATIONAL CONFERENCE
PCOS - UNRAVELING THE ENIGMA

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

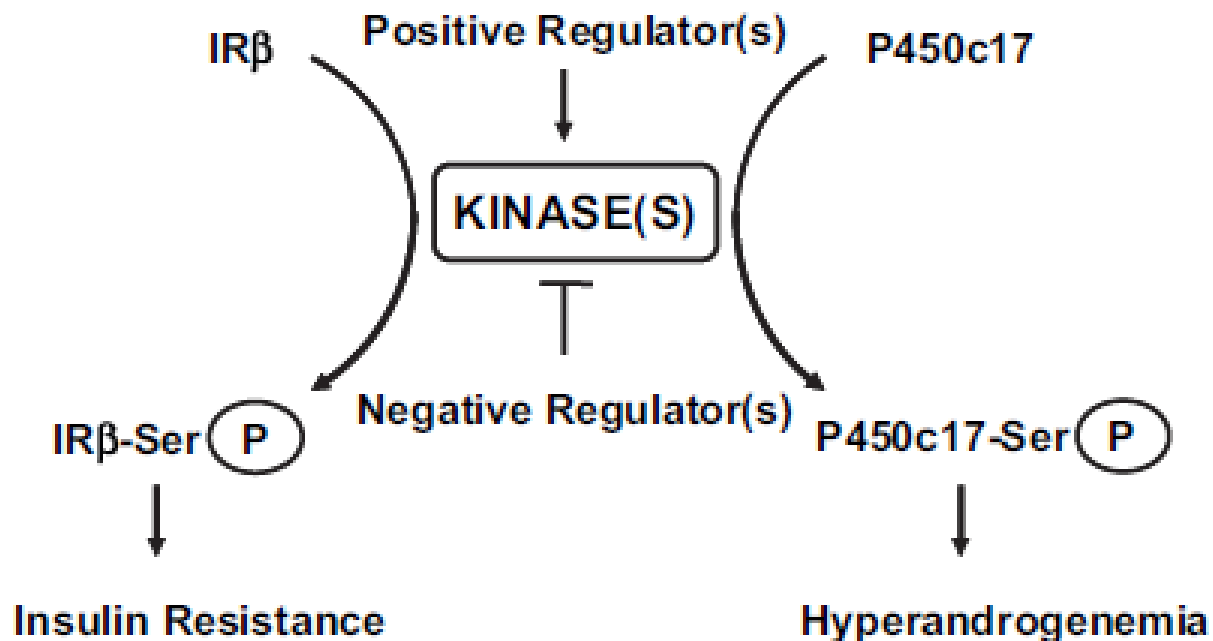
Dates: June 16 - 18, 2017 Bengaluru

The differential effects of tyrosine (Tyr) vs. serine (Ser) phosphorylation of the IR. Tyrosine phosphorylation of IR β after the binding of insulin to IR α leads to tyrosine phosphorylation of IRS-1 and the activation of downstream effector molecules. However, serine phosphorylation of IR β inhibits IRS-1 activation.



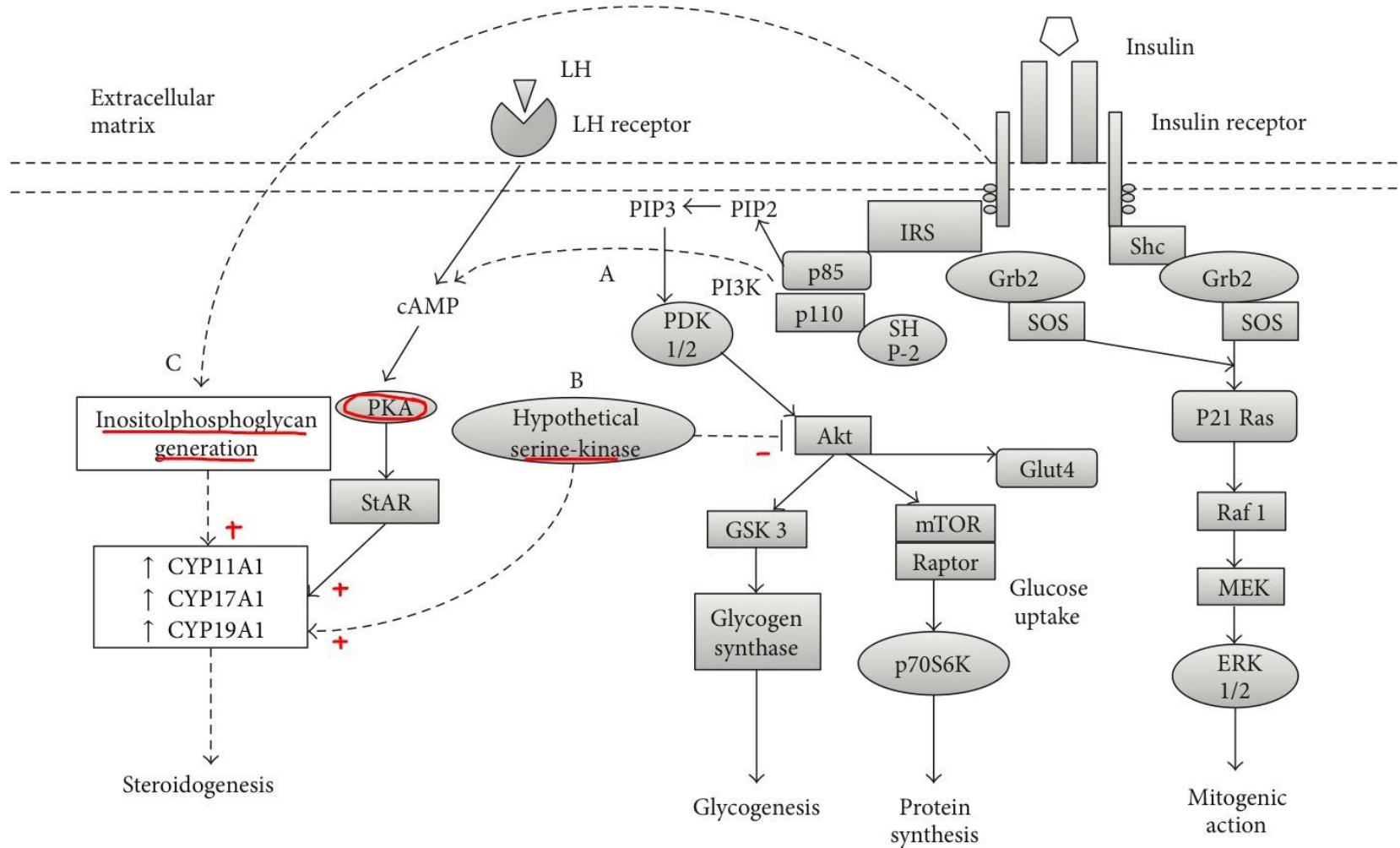
Bremer. Serine phosphorylation hypothesis of PCOS. Fertil Steril 2008.

The serine phosphorylation hypothesis. The serine phosphorylation hypothesis proposes that a dominantly inherited kinase (or kinases) serine phosphorylates both IR β and P450c17, leading to insulin resistance and increased androgen production, respectively. Both positive and negative regulatory factors may modulate kinase activity.



Bremer. Serine phosphorylation hypothesis of PCOS. Fertil Steril 2008.

INSULIN SIGNALING IN OVARIAN TISSUE AND SELECTIVE INSULIN RESISTANCE



USE OF SENSITIZERS/DIAZOXIDE/SS

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

Dates: June 16 - 18, 2017 Bengaluru

Dates: June 16 - 18, 2017 Bengaluru

- ◆ Decrease in insulin levels -by metformin/TZD ,or diazoxide or somatostatin –significantly reduce androgen levels in PCOS women.
- ◆ There was improvement in 17-20 lyase activity.
- ◆ Decrease in DHEAS levels

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

Dates: June 16 - 18, 2017 Bengaluru

DOES HYPERANDROGENEMIA LEAD TO HYPERINSULINEMIA?

◆ Testosterone or DHEAS signaling - upregulation of beta 3 adrenergic receptors and hormone-sensitive lipase expression in visceral adipose tissue (VAT)

◆ Increases lipolytic activity and release of FFA into circulation

◆ FFAs activate PKC, a serine/threonine kinase

◆ This leads to serine threonine kinase activation - inhibition of insulin signalling

◆ Hyperandrogenemia decreases the amount of type I muscle fibers, which are highly oxidative and insulin-sensitive.

◆ Increases type II fibers, which are glycolytic and less sensitive, as well as decreasing expression of glycogen synthase

◆ Androgen-driven pro inflammatory cytokine secretion from VAT and androgen-induced interference of insulin signalling.

◆ HA – associated with abdominal fat accumulation in women and lower levels of circulating SHBG and also lower adiponectin levels.

GnRH pulses
Rapid

LH /FSH
ratio
increased

Ovarian theca cell
androgen production
Decreased granulosa
cell aromatisation

Hyperinsulinemia (insulin
receptor defect/ binding
defect/ post receptor defect)

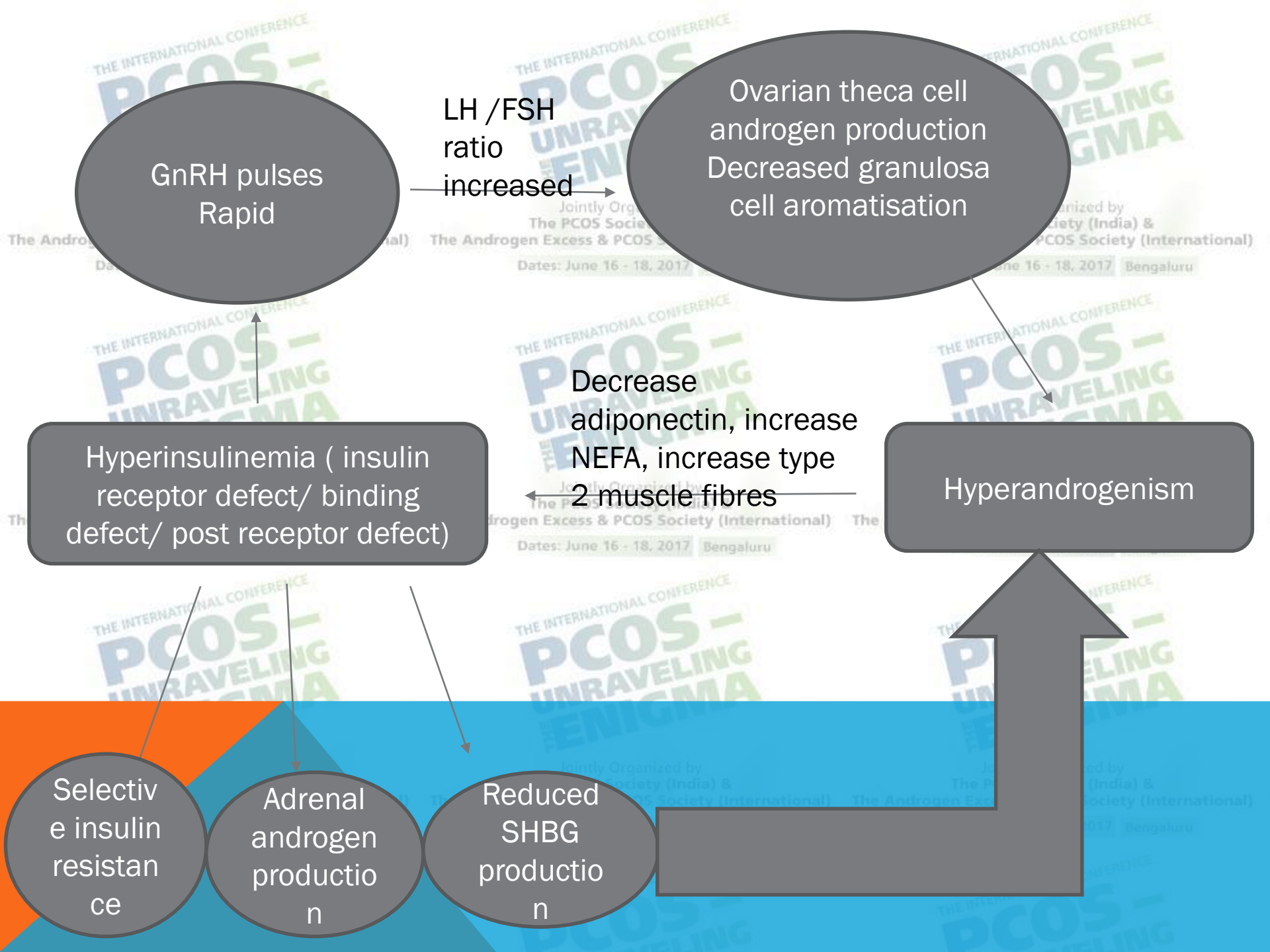
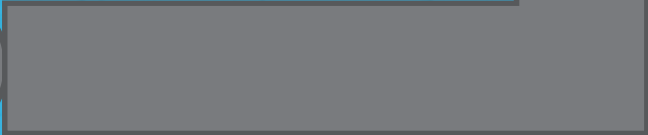
Decrease
adiponectin, increase
NEFA, increase type
2 muscle fibres

Hyperandrogenism

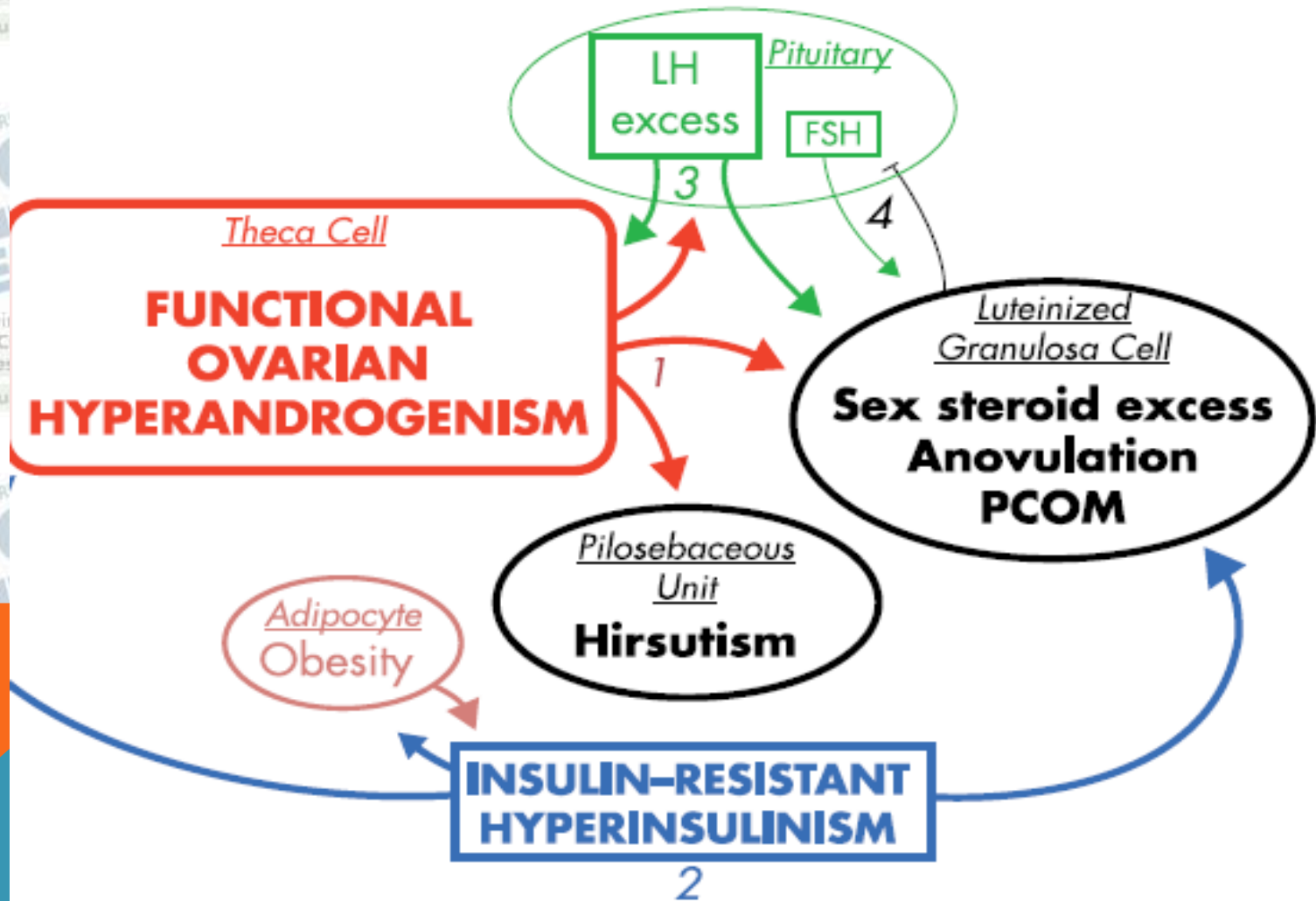
Selectiv
e insulin
resistan
ce

Adrenal
androgen
productio
n

Reduced
SHBG
productio
n



MINIMAL MODEL OF PCOS PATHOPHYSIOLOGY



THE INTERNATIONAL CONFERENCE
**PCOS -
UNRAVELING
THE ENIGMA**

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

THE INTERNATIONAL CONFERENCE
**PCOS -
UNRAVELING
THE ENIGMA**

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

THE INTERNATIONAL CONFERENCE
**PCOS -
UNRAVELING
THE ENIGMA**

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

THE INTERNATIONAL CONFERENCE
**PCOS -
UNRAVELING
THE ENIGMA**

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

THE INTERNATIONAL CONFERENCE
**PCOS -
UNRAVELING
THE ENIGMA**

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

THE INTERNATIONAL CONFERENCE
**PCOS -
UNRAVELING
THE ENIGMA**

Jointly Organized by
The PCOS Society (India) &
The Androgen Excess & PCOS Society (International)

Dates: June 16 - 18, 2017 Bengaluru

THANKYOU

