



# Tocolytics and Oxytocin

Lecture

By

**Mohammed M. Alanazi, B.Pharm, Ph.D**

Assistant Professor

Department of Pharmacology and Toxicology

College of Pharmacy, KSU

Slides adopted from Dr. Yeldez Bassiouni

College of Dentistry, 1<sup>st</sup> floor \ office 1A 29, momalanazi@ksu.edu.sa

# Objectives

- At the end of the lectures, students should be able to know and understand the:
  1. Drugs used to induce & augment labor.
  2. Drugs used to control post partum hemorrhage.
  3. Drugs used to induce pathological abortion.
  4. Drugs used to arrest premature labor.
  5. The mechanism of action and adverse effects of each drug.

# DRUGS PRODUCING UTERINE CONTRACTIONS (Oxytocic Drugs )

## 1. OXYTOCIN

- a) Syntocinon

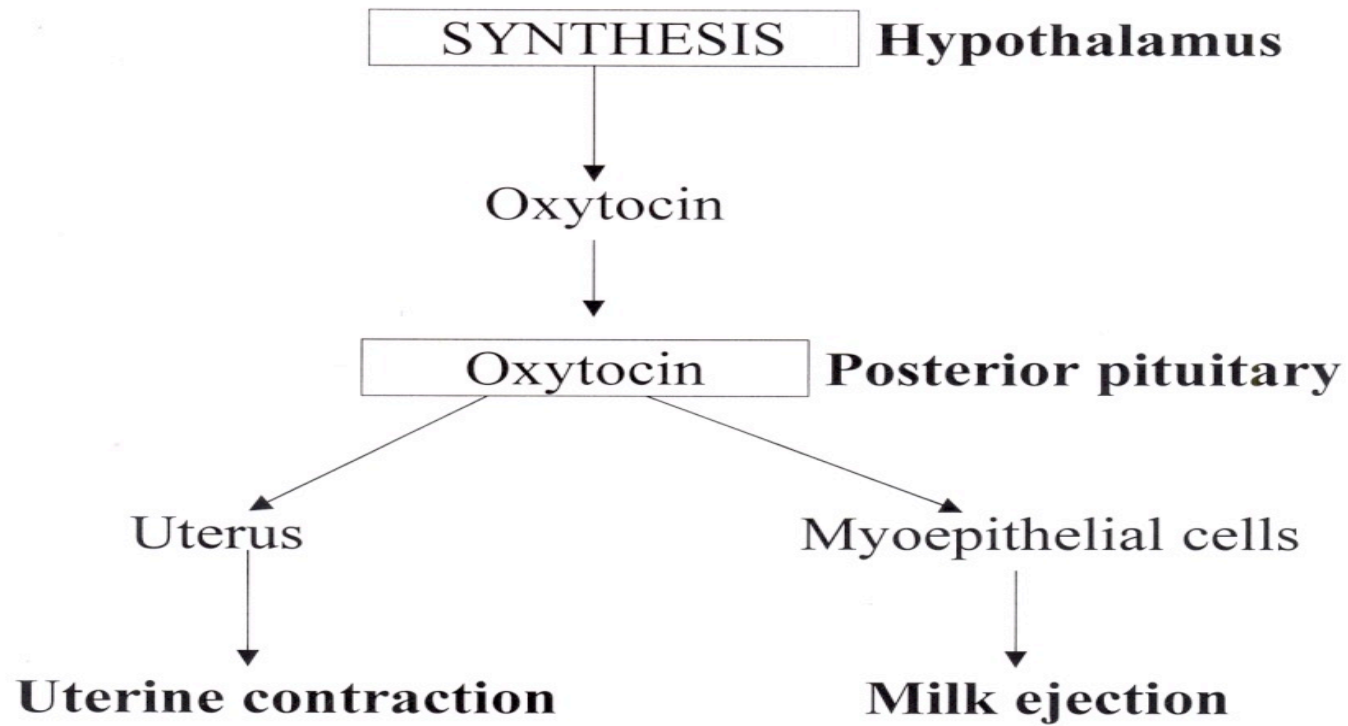
## 2. ERGOT ALKALOIDS

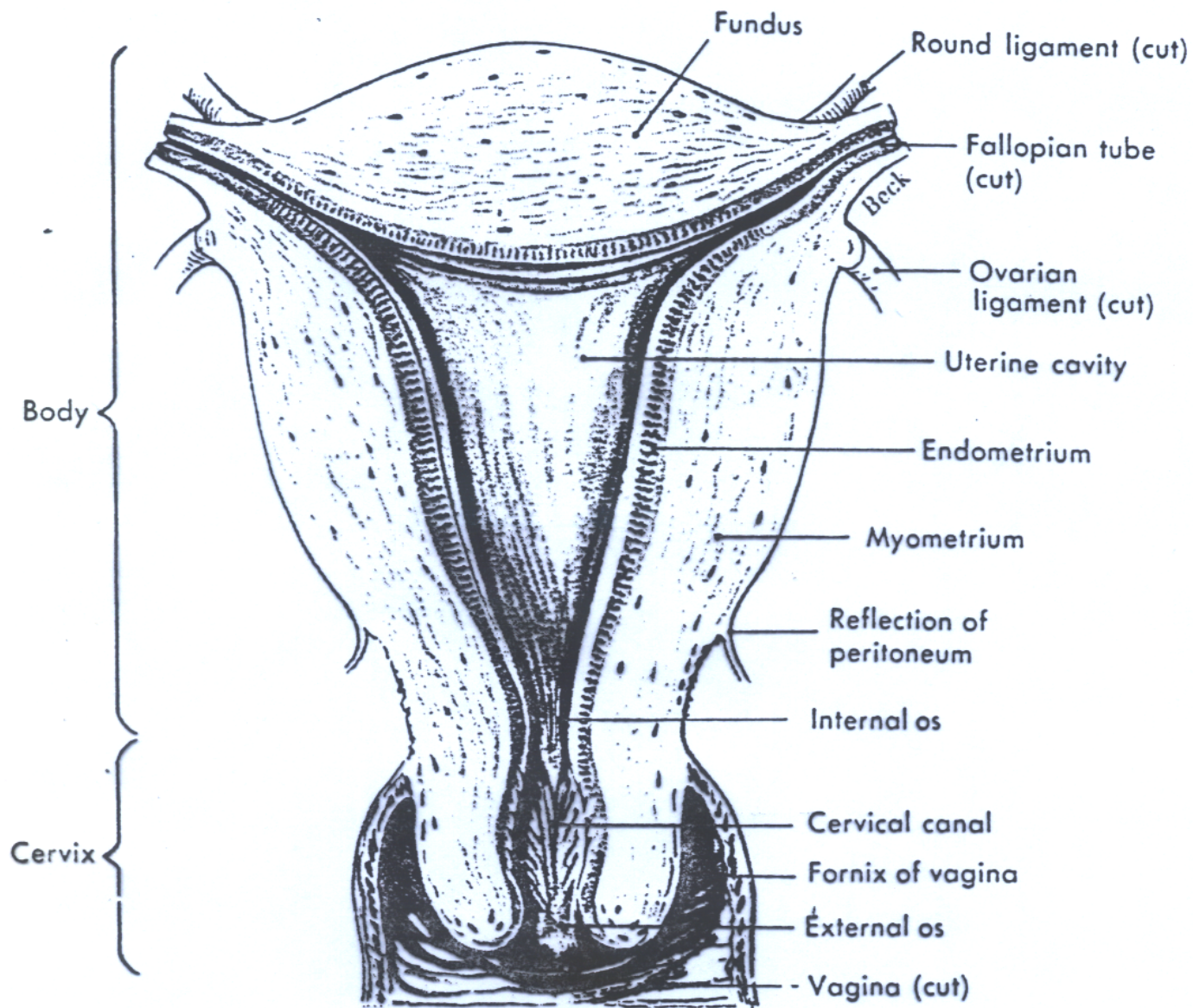
- a) Ergometrine (Ergonovine)
- b) Methyl ergometrine (methyl ergonovine)

## 3. PROSTAGLANDINS

- a) PGE<sub>2</sub>
- b) PGF<sub>2</sub> $\alpha$
- c) PGE<sub>1</sub>(misoprostol)

# OXYTOCIN





# Role of oxytocin

## Uterus

- Stimulates both the **frequency and force** of uterine contractility particularly of the **fundus** segment of the uterus.
- These contractions resemble the normal physiological contractions of uterus (**contractions followed by relaxation**)

## Role of oxytocin (cont.)

- **Immature uterus** is resistant to oxytocin.
- **Contract uterine smooth muscle only at term.**
- Sensitivity increases to 8 folds in last 9 weeks and 30 times in early labor.
- Clinically oxytocin is given only when uterine **cervix is soft and dilated.**

# Role of oxytocin

## Myo-epithelial cells

- Oxytocin contracts myoepithelial cells surrounding mammary alveoli in the breast & leads to **milk ejection**.



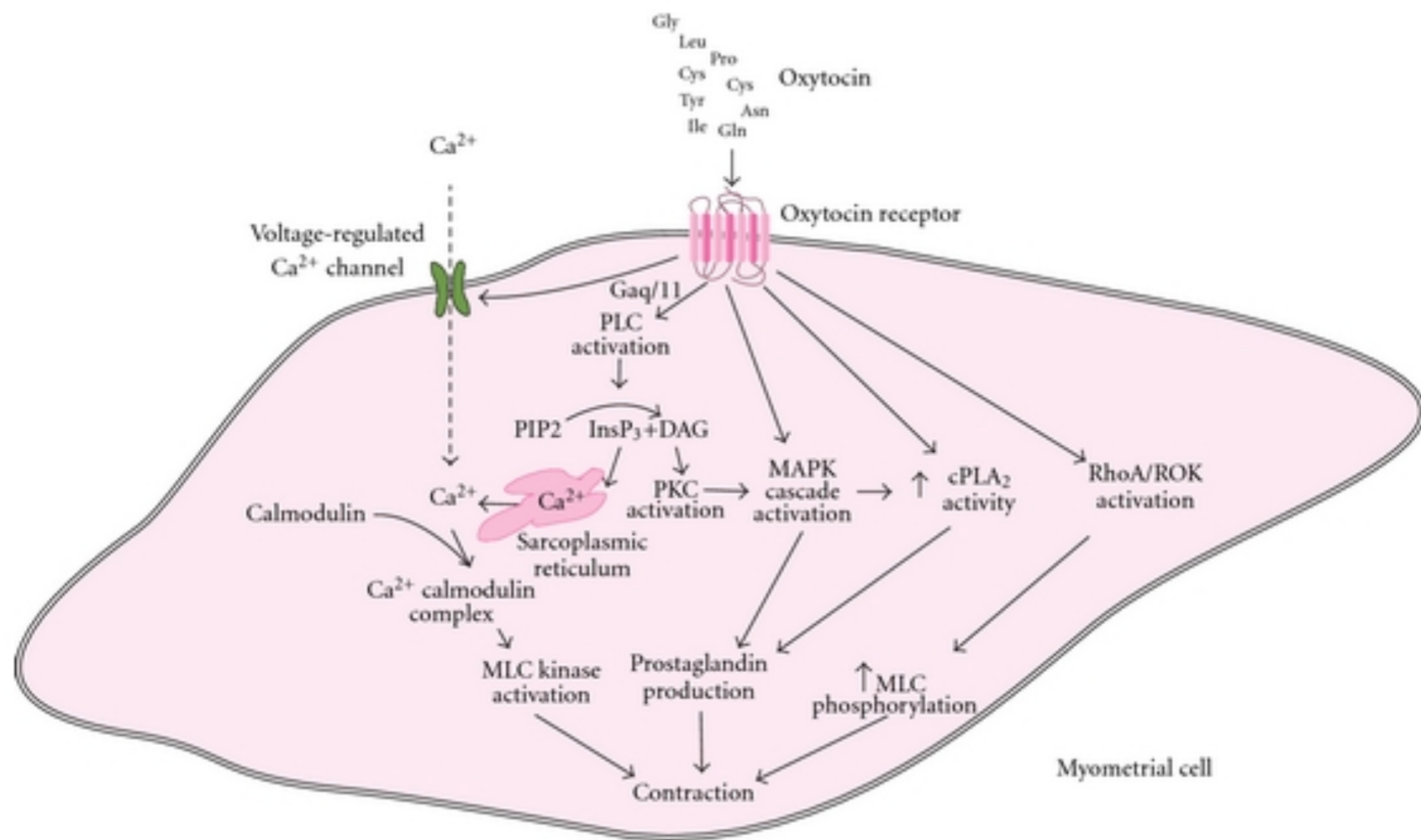
# Pharmacokinetics of oxytocin

- Absorption, Metabolism and Excretion
- **Not effective orally** (destroyed in GIT)
- Administered **i.v.** (augment labor)
- Also as **nasal spray** (impaired milk ejection)
- Not bound to plasma proteins
- Catabolized by liver & kidneys
- Half life = 5 minutes

# Mechanism of action

- The interaction of endogenous or administered oxytocin , with **myometrial cell membrane receptor** promotes the influx of  $\text{Ca}^{++}$  from extra cellular fluid and from S.R. into the cell , this increase in cytoplasmic calcium , stimulates uterine contraction .

S.R. Sarcoplasmic Reticulum



# Therapeutic Uses of Oxytocin

- Synthetic preparations of oxytocin; e.g. syntocinon are preferred.

## 1. Induction & augmentation of labor\* (slow I.V infusion)

- a) Mild preeclampsia near term
- b) Uterine inertia
- c) Incomplete abortion
- d) Post maturity
- e) Maternal diabetes

# Therapeutic Uses of Oxytocin

## 2. Post partum uterine hemorrhage (I.V drip)

(ergometrine is often used ??)

## 3. Impaired milk ejection

One puff in each nostril 2-3 min before nursing

# Oxytocin Side Effects

- **Maternal death due to hypertension**
- **Uterine rupture**
- **Fetal death (ischemia)**
- **Water intoxication if oxytocin is given with relatively large volumes of electrolyte-free aqueous fluid intravenously**

# Oxytocin Contraindications

- Hypersensitivity
- Prematurity
- Abnormal fetal position
- Evidence of fetal distress
- Cephalopelvic disproportion
- Incompletely dilated cervix

# Oxytocin Precautions

- Multiple pregnancy
- Previous c- section
- Hypertension



# Ergot Alkaloids

## Natural

- Ergometrine (Ergonovine)

## Synthetic

- Methyl ergometrine (Methylergonovine)

# Effects on the Uterus

- Ergot alkaloids induce **TETANIC CONTRACTION** of uterus without relaxation in between (not like normal physiological contractions)
- It causes contractions of uterus as a whole i.e. fundus and cervix (tend to compress rather than to expel the fetus)
- **Difference between oxytocin & ergots??**

# Ergot alkaloids (pharmacokinetics)

- **Absorption, fate and excretion**
- Usually given I.M
- Extensively metabolized in liver
- 90% of metabolites are excreted in bile

# Clinical uses

- Post partum hemorrhage (3<sup>rd</sup> stage of labor)\*\*

**When to give it?**

- Preparations:

Syntometrine (ergometrine 0.5 mg + oxytocin 5.0 I.U) , I.M.

# **Ergot alkaloids Side effects**

- **Nausea, vomiting, diarrhea**
- **Hypertension**
- **Vasoconstriction of peripheral blood vessels (toes & fingers)**
- **Gangrene**

# Ergot Contraindications:

## 1. Induction of labor

- a) 1<sup>st</sup> and 2<sup>nd</sup> stage of labor
- b) vascular disease
- c) Severe hepatic and renal impairment
- d) Severe hypertension

# PROSTAGLANDINS

- PGE2 – Dinoprostone
  - Vaginal suppository.
  - Extra- amniotic solution
- PGF2 $\alpha$ - Dinoprost, Carboprost
  - Intra-amniotic injection
- Misoprostol (synthetic PGE1)

# Prostaglandins therapeutic uses

- **Induction of abortion (pathological)\*\***
- **Induction of labor (fetal death in utero)**
- **Postpartum hemorrhage**



# Difference between PGs and Oxytocin:

- PGs contract uterine smooth muscle not only at term(as with oxytocin), but **throughout pregnancy**.
- **PGs soften the cervix**; whereas oxytocin does not.
- **PGs have longer duration** of action than oxytocin.

# Prostaglandins side effects

- Nausea , vomiting
- Abdominal pain
- Diarrhea
- Bronchospasm (PGF2 $\alpha$ )
- Flushing (PGE2)

# Prostaglandins

## • Contraindications:

- Mechanical obstruction of delivery
- Fetal distress
- Predisposition to uterine rupture

## • Precautions:

- Asthma
- Multiple pregnancy
- Glaucoma
- Uterine rupture

# Difference between Oxytocin and Prostaglandins

<b>Character</b>	<b>Oxytocin</b>	<b>Prostaglandins</b>
<b>Contraction</b>	<ul style="list-style-type: none"><li>• Only at term</li></ul>	<ul style="list-style-type: none"><li>• Contraction through out pregnancy</li></ul>
<b>Cervix</b>	<ul style="list-style-type: none"><li>• Does not soften the cervix</li></ul>	<ul style="list-style-type: none"><li>• soften the cervix</li></ul>

## Difference (cont'd)

<b>Character</b>	<b>Oxytocin</b>	<b>Prostaglandins</b>
<b>Duration of action</b>	<ul style="list-style-type: none"><li>• Shorter</li></ul>	<ul style="list-style-type: none"><li>• Longer</li></ul>
<b>Uses</b>	<ul style="list-style-type: none"><li>• Induce and augment labor and post partum hemorrhage</li></ul>	<ul style="list-style-type: none"><li>• Induce abortion in 2<sup>nd</sup> trimester of pregnancy.</li><li>• Used as vaginal suppository for induction of labor</li></ul>

# Difference b/w Oxytocin and Ergometrine

<b>Character</b>	<b>Oxytocin</b>	<b>Ergometrine</b>
<b>Contractions</b>	<ul style="list-style-type: none"><li>• Resembles normal physiological contractions</li></ul>	<ul style="list-style-type: none"><li>• Tetanic contraction ; doesn't resemble normal physiological contractions</li></ul>
<b>Uses</b>	<ul style="list-style-type: none"><li>• To induce &amp; augment labor.</li><li>• *Post partum hemorrhage</li></ul>	<ul style="list-style-type: none"><li>• Only in postpartum hemorrhage</li></ul>
<b>Onset and Duration</b>	<ul style="list-style-type: none"><li>• Rapid onset</li><li>• Shorter duration of action</li></ul>	<ul style="list-style-type: none"><li>• Moderate onset</li><li>• Long duration of action</li></ul>

# **UTERINE RELAXANTS**

# DRUGS PRODUCING UTERINE RELAXATION (Tocolytic Drugs )

- Action and Uses:

Relax the uterus and arrest threatened abortion or delay premature labor.

- **$\beta$ -Adrenoceptor agonists\*\***

- Ritodrine, i.v. drip
- Selective  $\beta_2$  receptor agonist used specifically as a uterine relaxant.



# $\beta$ - adrenoceptor agonists

- Mechanism of action

- Bind to  $\beta$ -adrenoceptors , activate enzyme Adenylate cyclase , increase in the level of cAMP reducing intracellular calcium level.

# **$\beta$ - adrenoceptor agonists Side Effects**

- Tremor
- Nausea , vomiting
- Flushing
- Sweating
- Tachycardia (high dose)
- Hypotension
- Hyperglycemia
- Hypokalemia

# **CALCIUM CHANNEL BLOCKERS**

- **Nifedipine**
- **Causes relaxation of myometrium**
- **Markedly inhibits the amplitude of spontaneous and oxytocin-induced contractions**

# **CALCIUM CHANNEL BLOCKERS Side effects**

- **Headache, dizziness**
- **Hypotension**
- **Flushing**
- **Constipation**
- **Ankle edema**
- **Coughing**
- **Wheezing**
- **Tachycardia**

# Atosiban

- **New tocolytic agent**
- **Compete with oxytocin at its receptors on the uterus.**
- **Given by IV infusion for 48 hrs**

**Questions???**