UNIVERSITÀ DEGLI STUDI DI PADOVA

Il latte: colpevole o assolto. La voce del veterinario

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ACNE Ferrara 2017
14° Meeting di aggiornamento su acne e dermatosi correlate
FERRARA, 24-25 novembre 2017

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Outline

1 **Hormones & ACNE**

2 **Hormones in Milk**

- Why measuring hormones in milk
- Hormones & Lactation
- Colostrum vs Milk

3 **Hormones in Milk vs. Hormones in Human Blood**

4 **Milk Hormones vs. Host Intestine**

Peptide Hormones (IGF-1) ⟷	IGF-1 absorption?
Steroid Hormones (E2 & DHEA) ⟷	Entero-Hepatic Circulation & Hormone inactivation

G.A.L.T. interaction

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Hormones & ACNE

Oestrogens

Androgens

Progesterone

Glucocorticoids

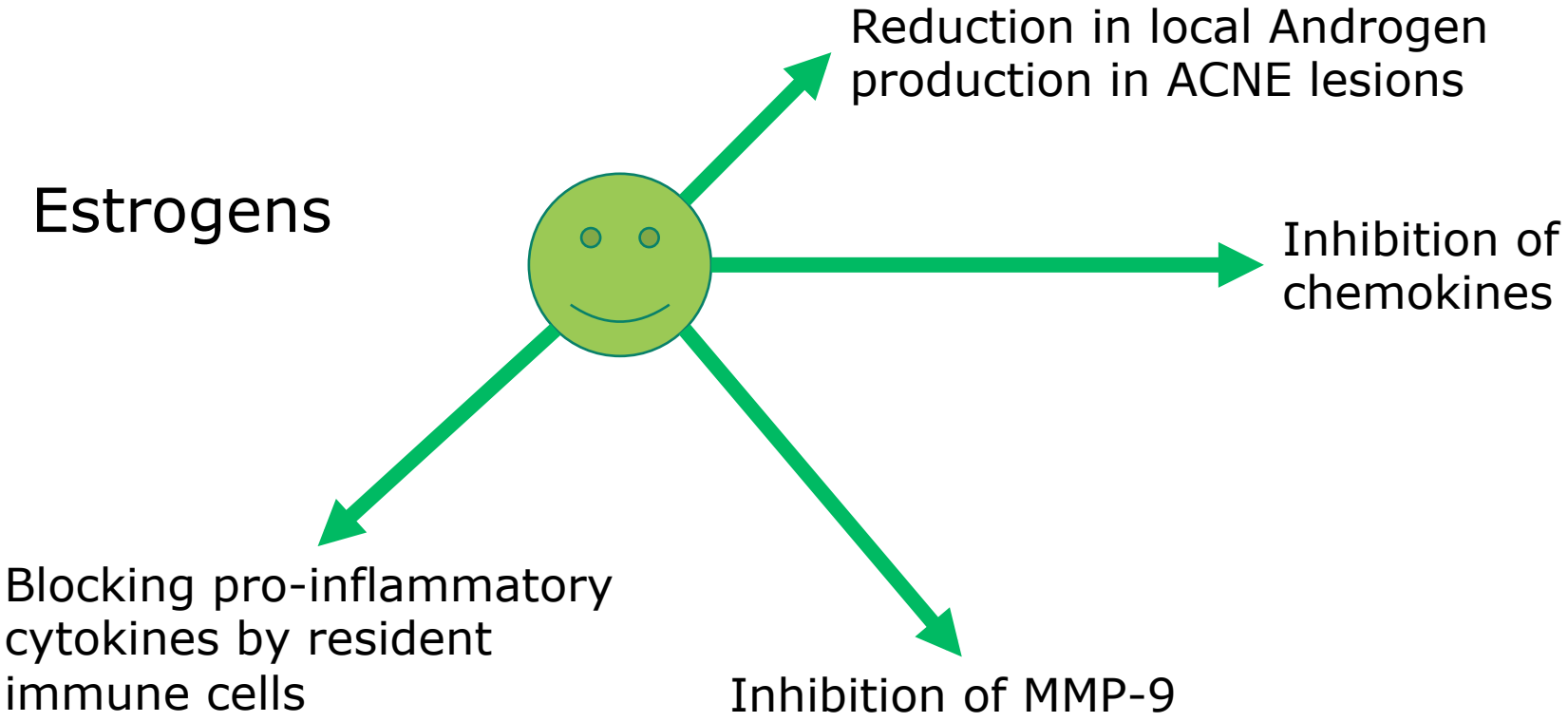
IGF-1

Sebo production during menstrual cycle?

Increase TLR2 expression & enhance immune response in skin? Local HPA axis!

Review by: Arora et al., 2011 – Clinical Biochem. 44, 1035-1040

Hormones & ACNE



Review by: Arora et al., 2011 – Clinical Biochem. 44, 1035-1040

Oestrogens in milk products

Product	Fat (%)	E2 (pg/mL)	E2/serving (ng)
Skim milk	< 0.05	0.4 ± 0.03	0.1 (237 mL)
Milk	1	0.6 ± 0.03	0.1 (237 mL)
Milk	2	0.9 ± 0.06	0.2 (237 mL)
Whole milk	3.25	1.1 ± 0.05	0.3 (237 mL)
Cream	36	6.0 ± 0.29	0.1 (15 mL)
Butter	80	15.8 ± 1.17	0.2 (14 g)

Pape-Zambito et al. 2010 – J. Dairy Sci. 93, 2533-2540

Hormones & ACNE

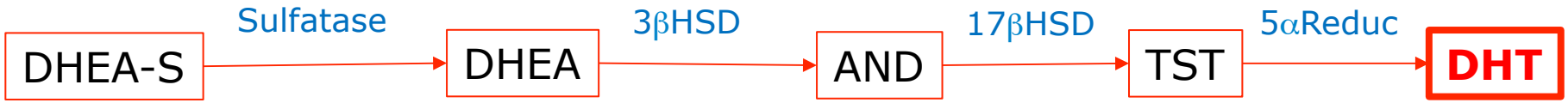
Androgens

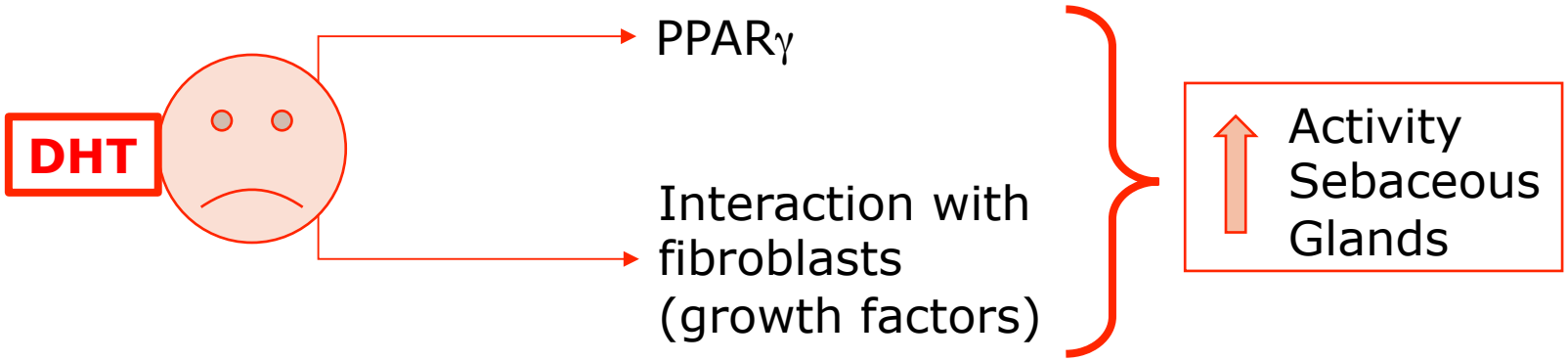
Higher Androgen in Blood

ACNE patients

Normal Androgen in Blood

More reactive sebaceous glands





Review by: Arora et al., 2011 – Clinical Biochem. 44, 1035-1040

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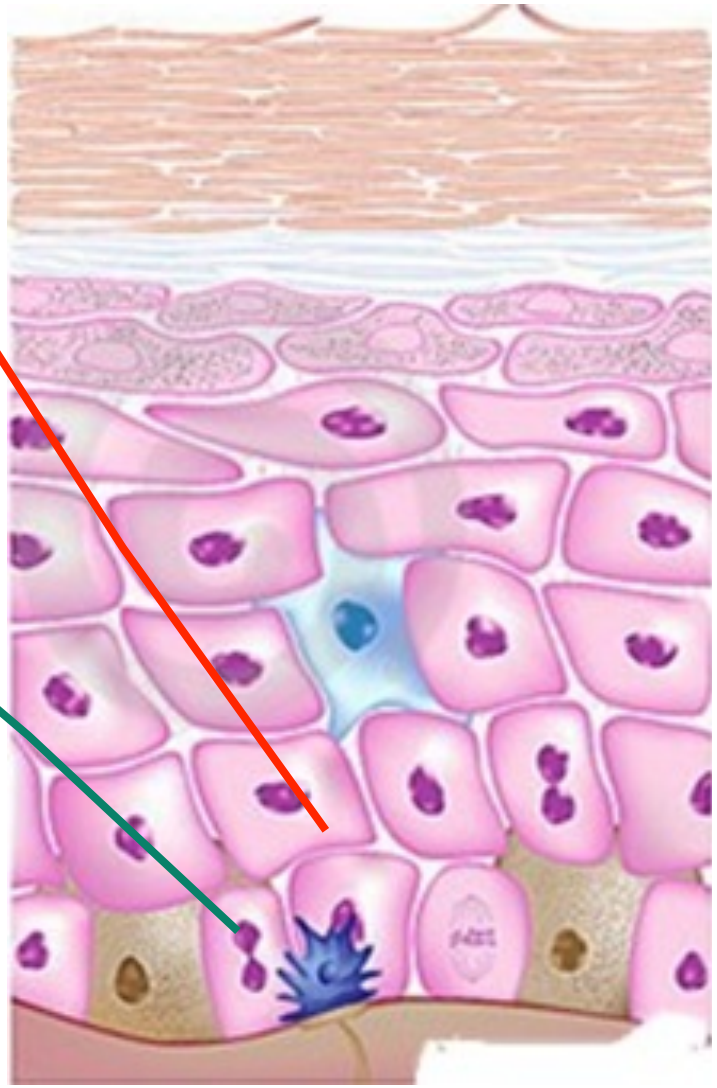
Growth Factors & Keratinocytes

Inhibit Growth:
1. TGFβ
2. Vitamin D3
3. INFγ

Promote Growth & Migration:
1. EGF
2. FGF
3. HGF
4. **IGF**
5. GM-CSF



s. corneum

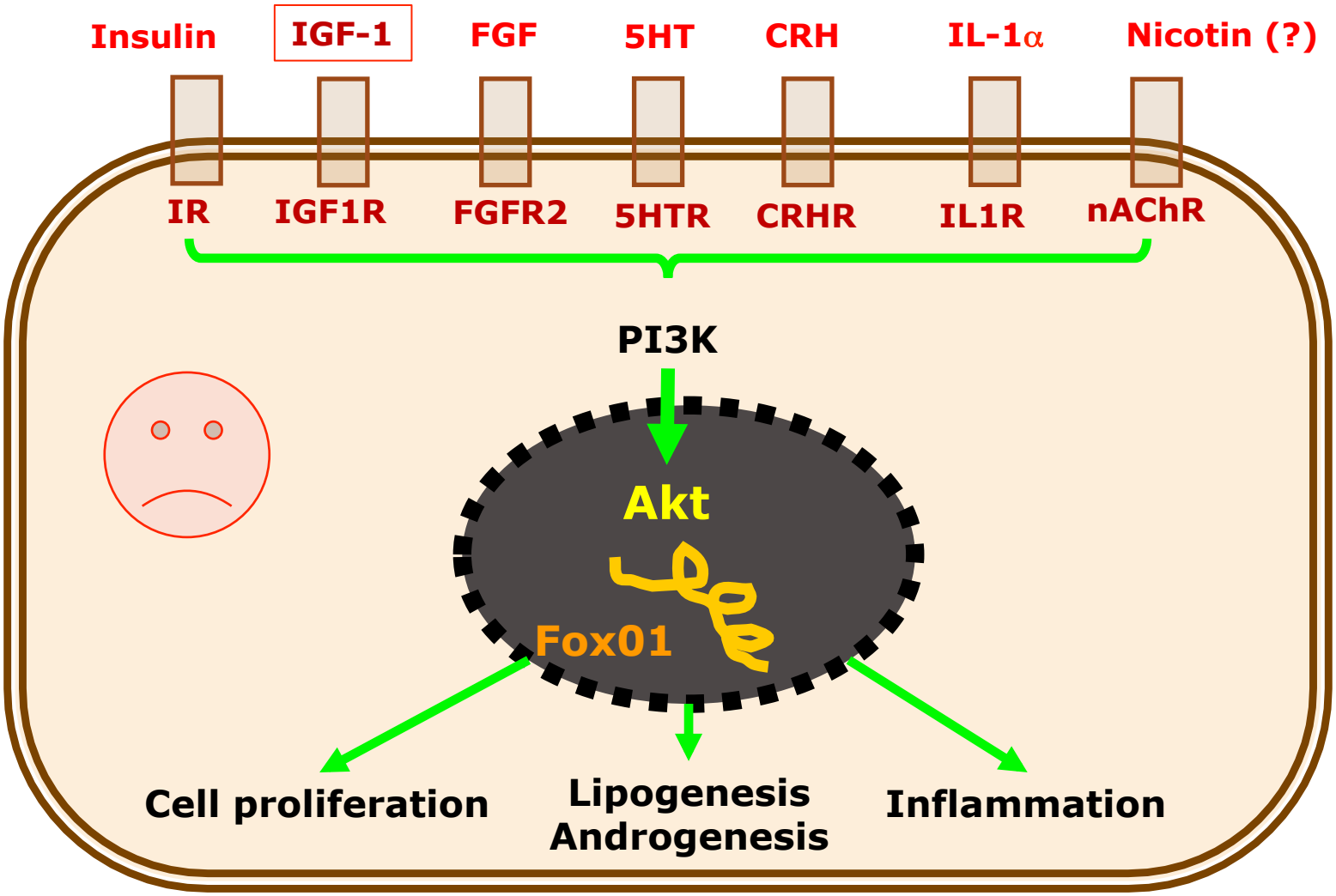
s. lucidum

s. granulosum

s. spinosum

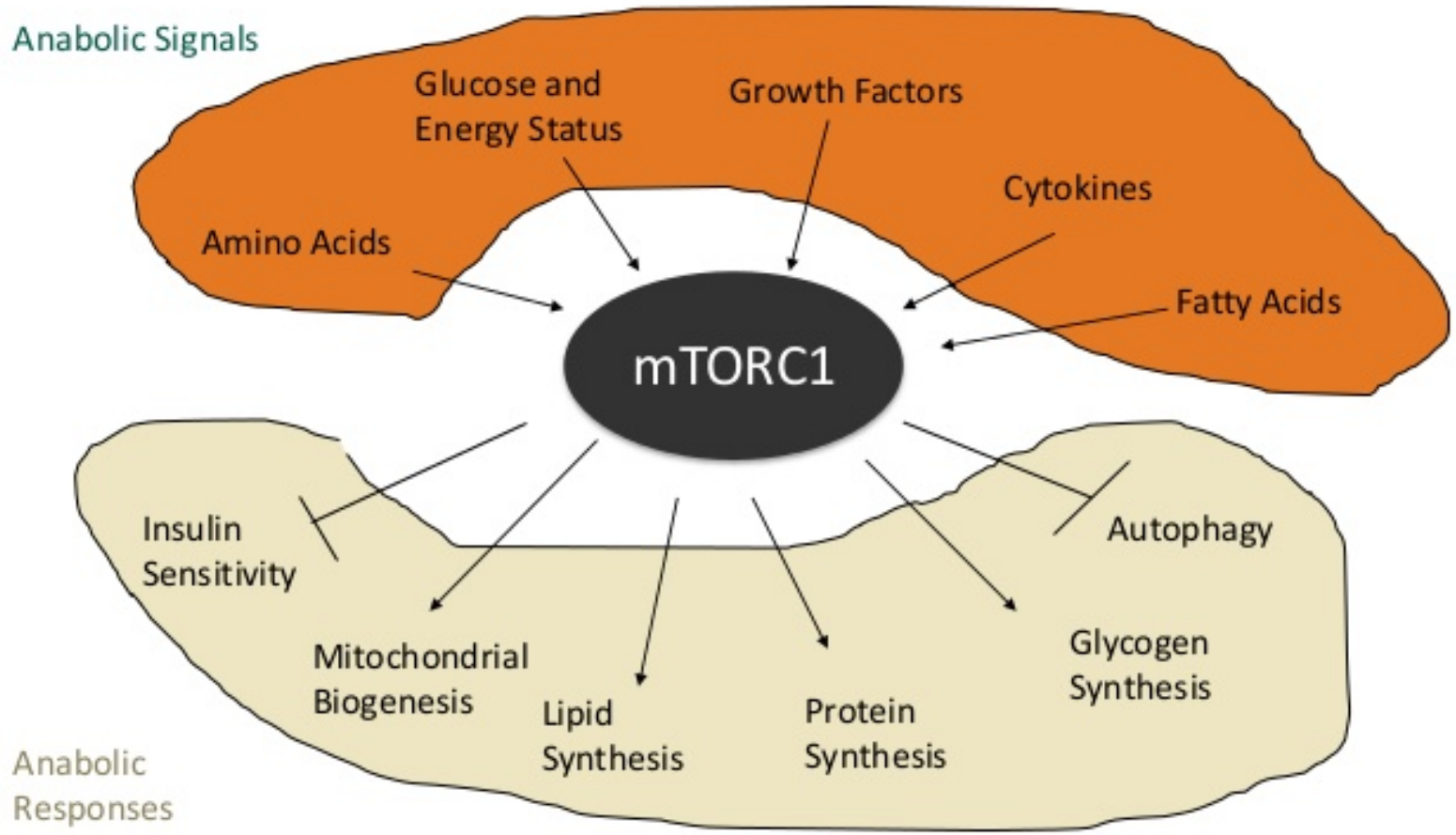
s. basale

Hormones & ACNE



Hormones & ACNE

What Does TORC1 Do?



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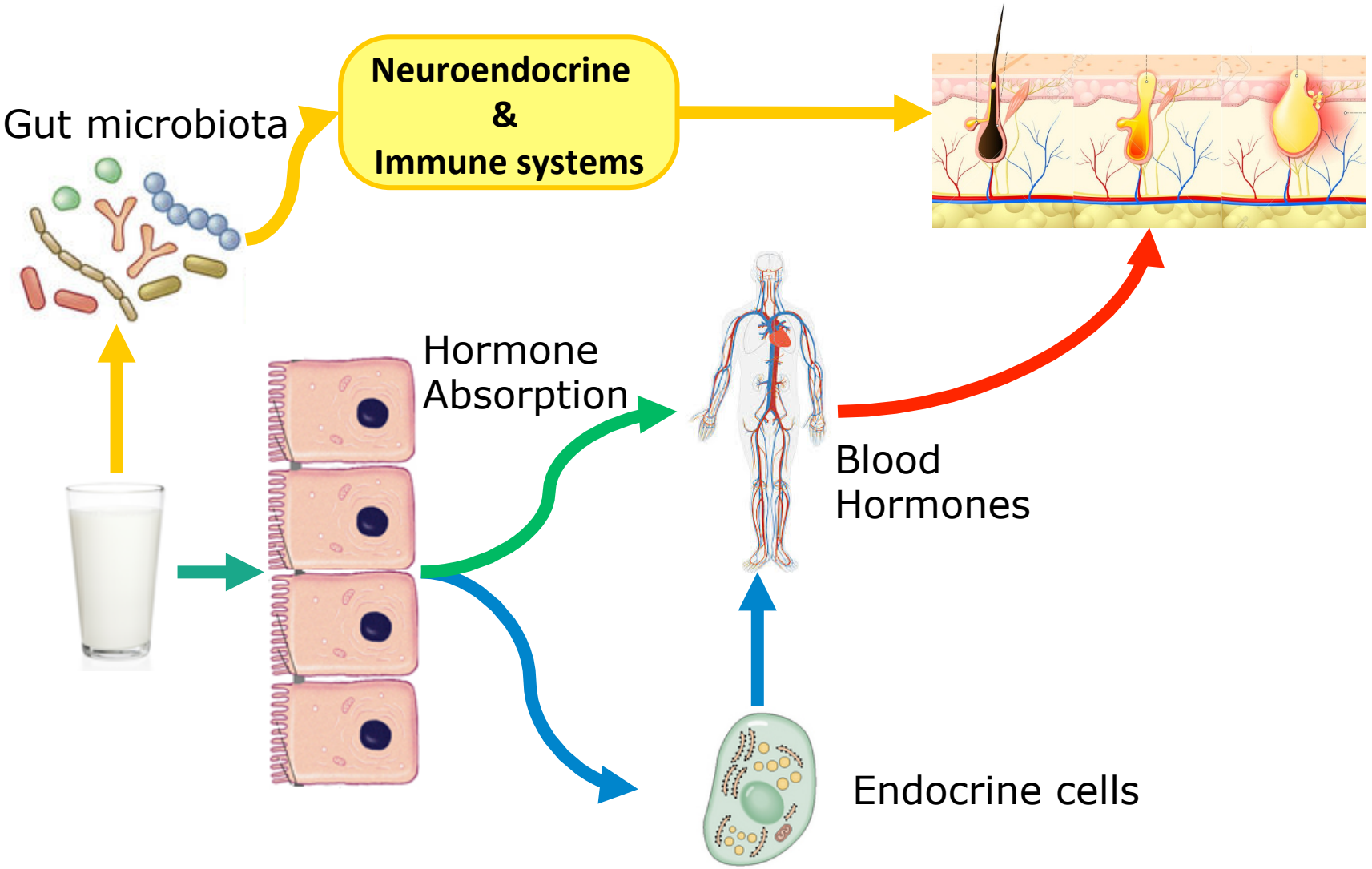
Can milk contribute to ACNE pathogenesis?



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Hormones in Milk, Mammary Gland Biology & Newborn Development

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Why Measuring Hormones in Milk?

Milk is a biological matrix alternative to blood

Monitoring reproductive activity/fertility	**E2; P4; (PAG)**
Monitoring metabolism	**IGF-1, Insulin, GH**
Monitoring "stress" & "welfare"	**HC; DHEA**
Monitoring immune status	**HC, Cytokines; TNFα**
Studying mammary biology	**PRL; PL; IGF-1; IGF-2**

Hormones in Milk

Hormones / Growth factors

Newborn

- Development:
  - Gastrointestinal tract
  - Immune system
  - Neuroendocrine system
- Metabolic functions

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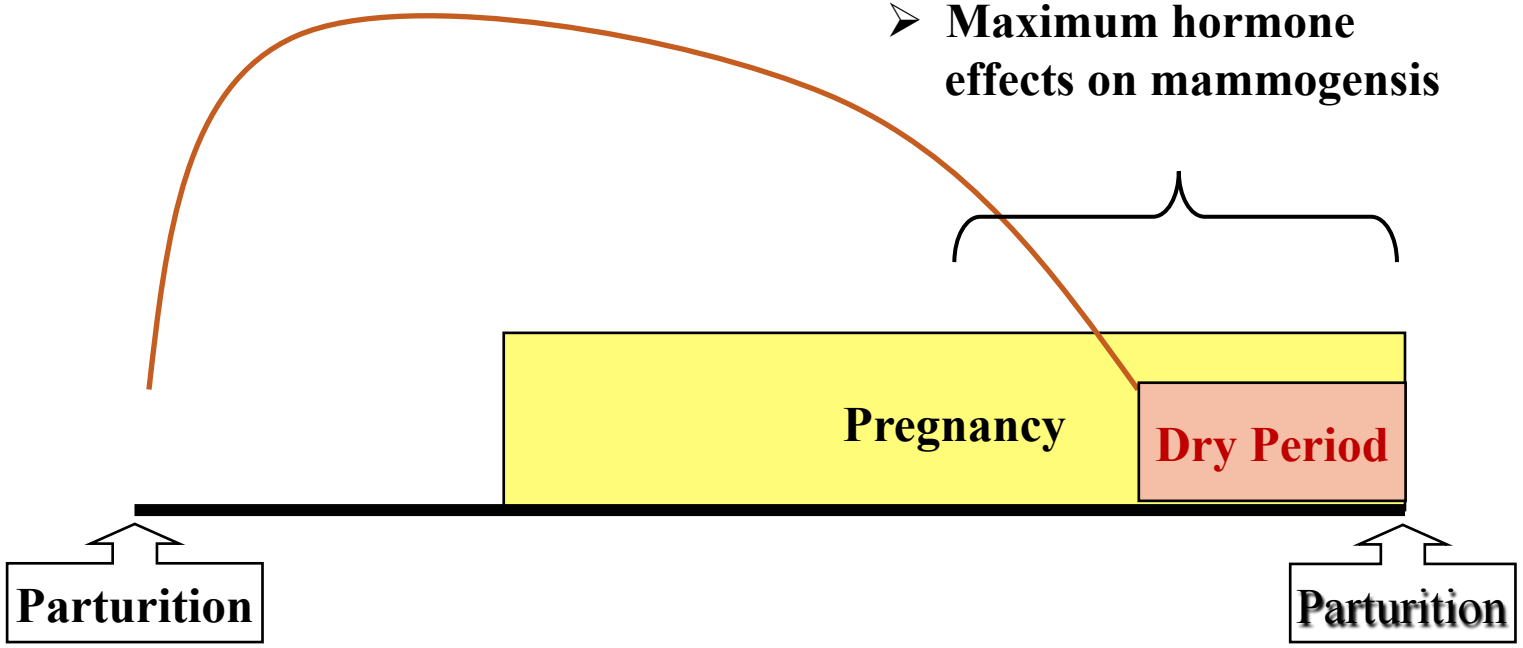
The cow's reproductive cycle

- Period of maximum placental oestrogen production
- Maximum hormone effects on mammogensis



The dairy cow is contemporarily pregnant during most lactation

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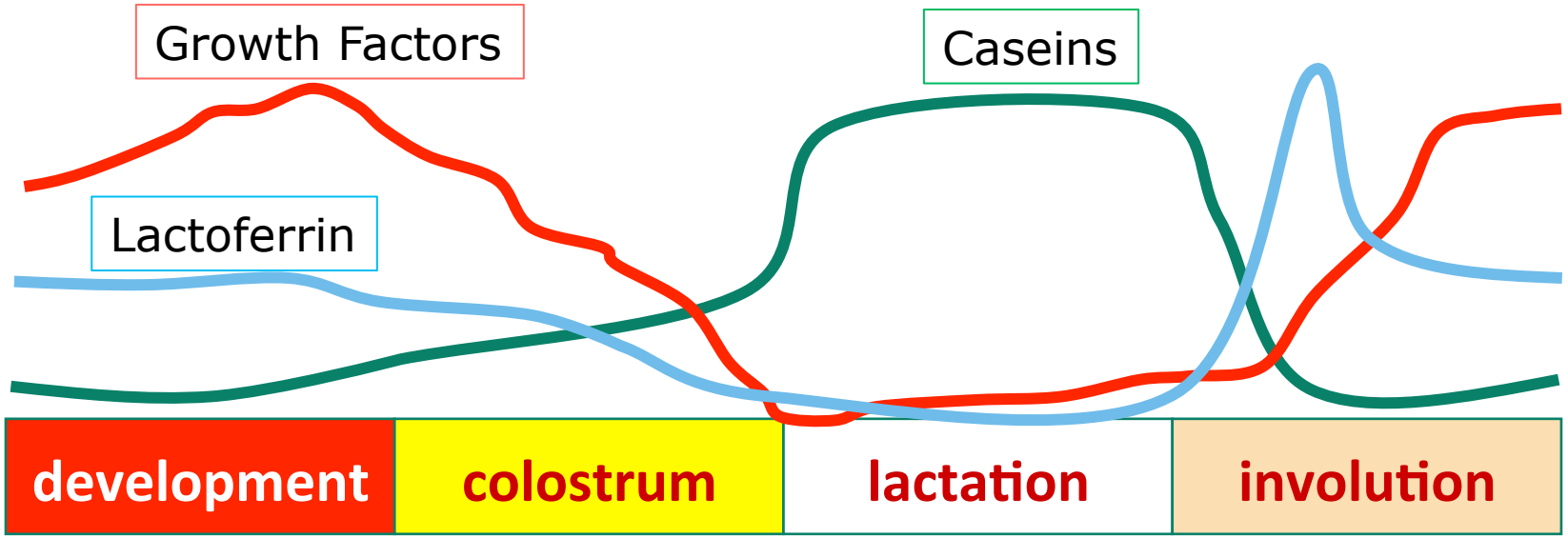
Proteins in Colostrum and Milk

***Growth Factors are low in milk**



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This sentence is true not only for oestrogens

"…, over the past recent years, concern has been raised about the possible adverse effect of milk-borne oestrogens by epidemiologically found correlations, but **without scientific evidence for a relationship**".

Malekinejad et al., 2006 – J. Agric. Food Chem, 54, 9785-9791

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IGF-1

Hormone	Colostrum (day 2) NOT SOLD	Mature milk (week 4) SOLD	
IGF-1 (ng/mL)	**103 ± 21**	**4 ± 1**	*Resistant to heat (pasteurization) & acid*
Insulin (ng/mL)	4.6 ± 1.0	0.4 ± 0.0	Several studies suggested that growth factors in colostrum (and milk) are important for the development of the newborn intestine.
TNF-a (ng/mL)	5.0 ± 0.6	1.8 ± 0.2	

Ontsouka et al., 2002 – J Dairy Sci, 86:2005-2011

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IGF-1

IGF-1 concentration in milk

Human	≈ 3.0 ng/ml	Milsom et al. 2008	Hormone Research, 69:307-311
Human	2.8 ng/ml	Elmlinger et al. 2007	Hormone Research, 68:124-131
Cow (ctrl)	2.8 ng/ml	Prosser et al. 1989	J Dairy Res, 56:17-26
(bST)	11.2 ng/ml		
Retail cow	3.1 ng/ml	Vicini et al. 2008	J Am Diet Ass, 108:1198-1203
Cow (ctrl)	3.9 ng/ml	Collier et al. 2008	Dom Anim Endocrinol, 35:16-23
(bST)	4.3 ng/ml		

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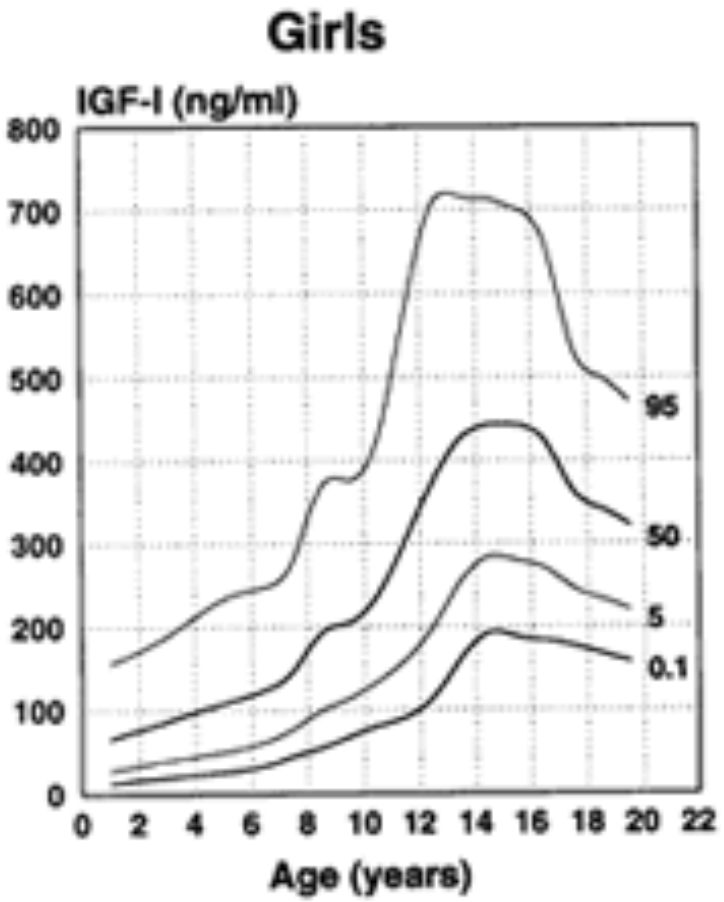
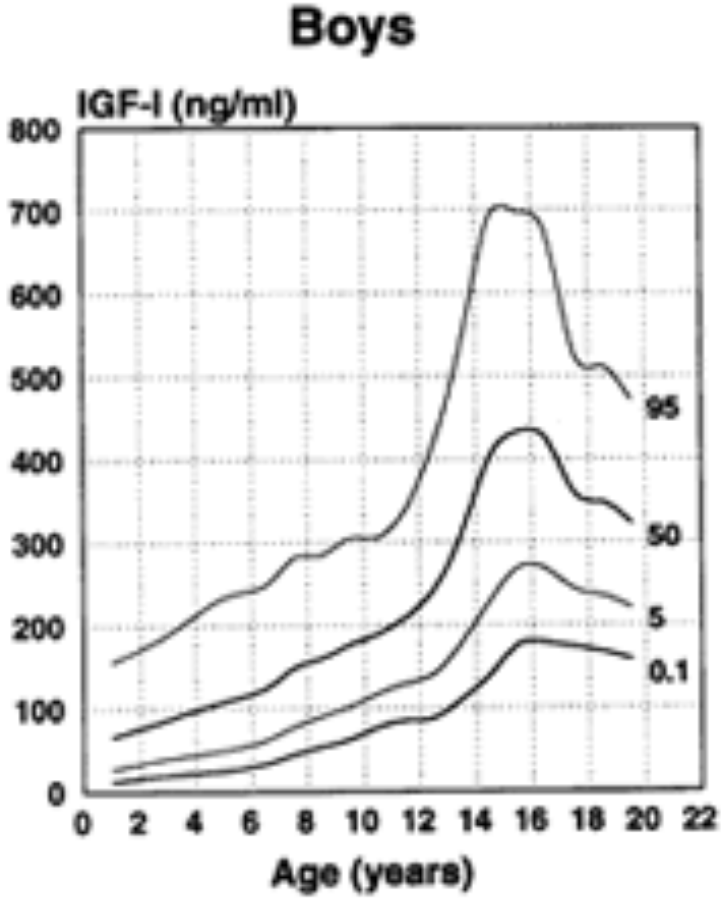
IGF-1





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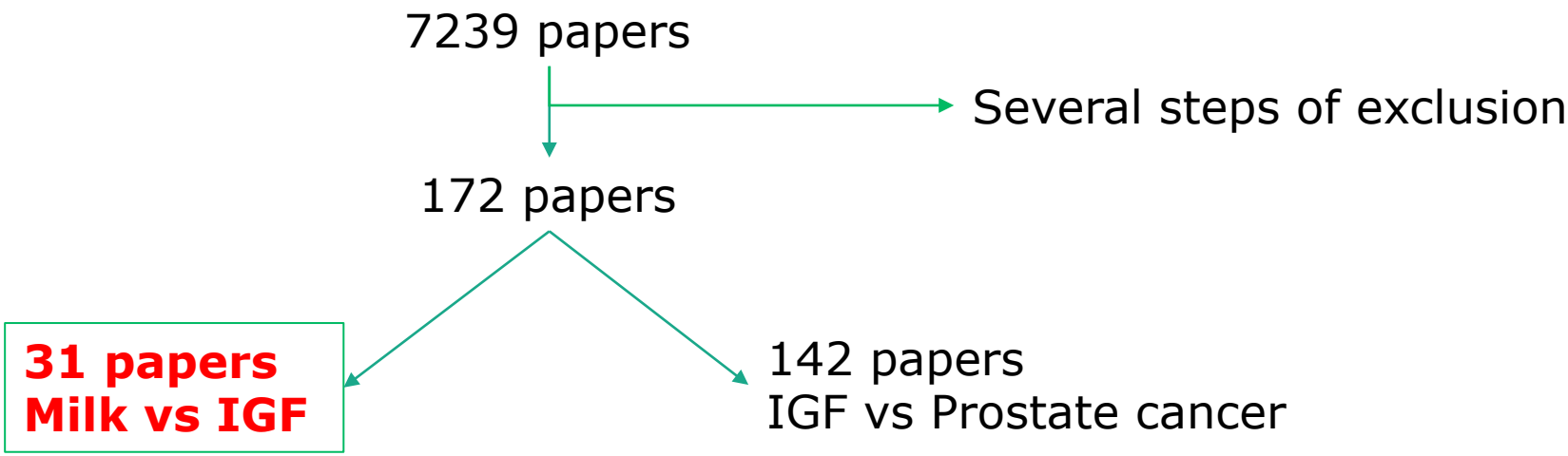
Milk & IGF-1 in Blood

Metanalysis by: Harrison et al., 2017, Cancer Causes Control 28, 497-528



There is moderate evidence that circulating IGF-1 and IGFBP-3 increase with milk (and dairy protein) intake.

Standardized effect:
0.1 SD increase in blood IGF-1 per **1 SD increase** in Milk intake

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Intestinal Absorption of Milk IGF-1?

"in vivo" experiment in **neonatal** subjects

Odle et al. 1996
J Anim Sci 74:2509-2522

NEONATES OF FARMED SPECIES (Review)

Xu & Wang 1996
J Pediatric Gastroenterology and Nutrition 23:430-437

PIGLETS

Vacher et al. 1995
Biology of the Neonate 68:354-367

CALVES

Intestinal Absorption of Milk IGF-1?

Kimura et al. 1997 - J Pharmacol Exp Therapeutics 283:611-618

Adult RATS "*ex vivo*"

IGF-1
200 μg/ml

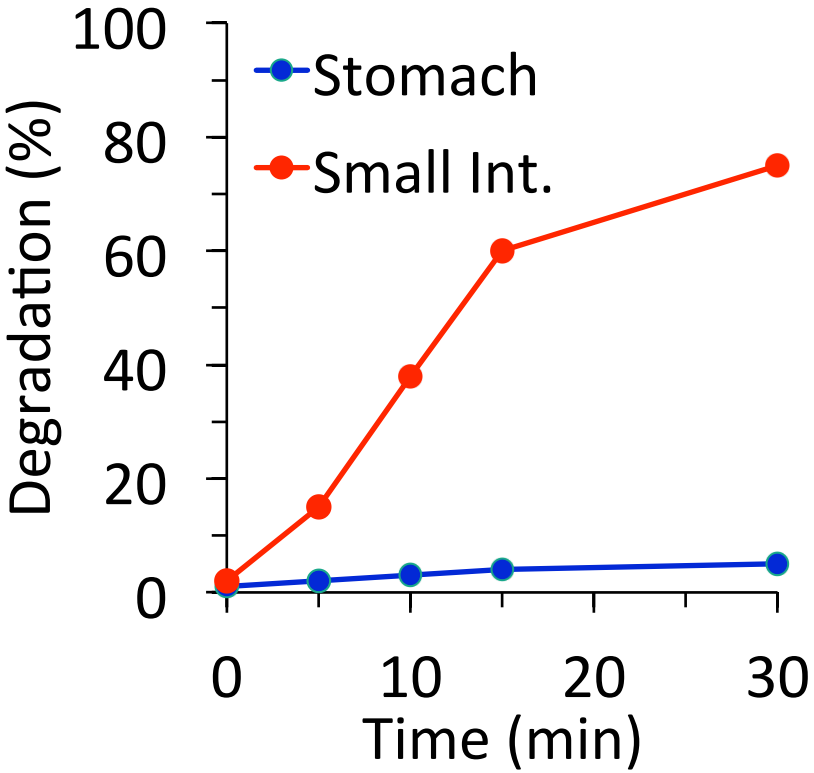
+ casein
0.2 g/100 ml

Alone

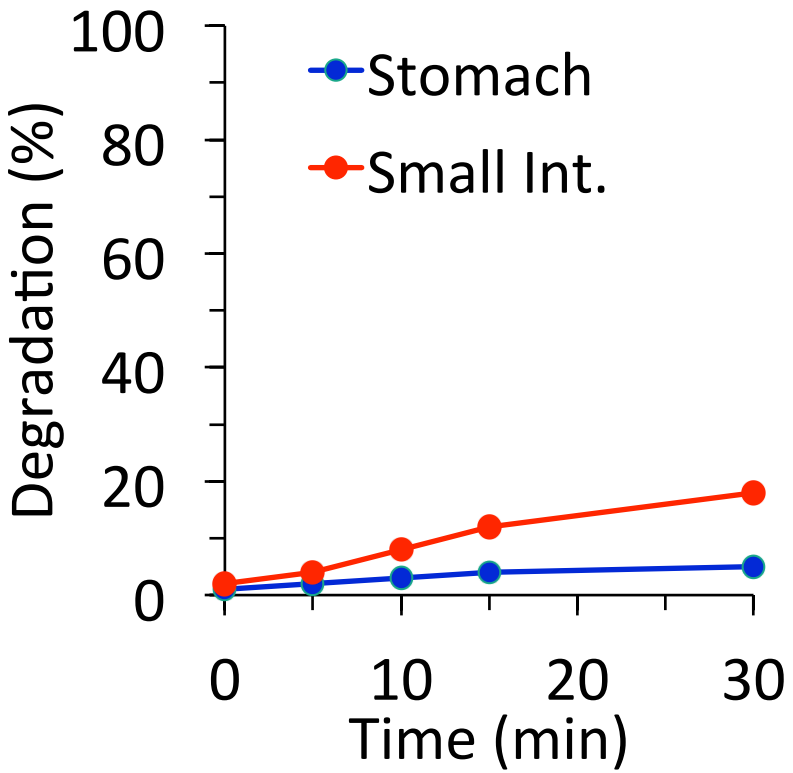
- **Degradation study**
- **Absorption studies**
  - Oral administration
  - *In situ* loop method
  - *In situ* single pass perfusion
  - *In vito* everted sac

Degradation of Milk IGF-1

Kimura et al. 1997
J Pharmacol Exp Therapeutics 283:611-618



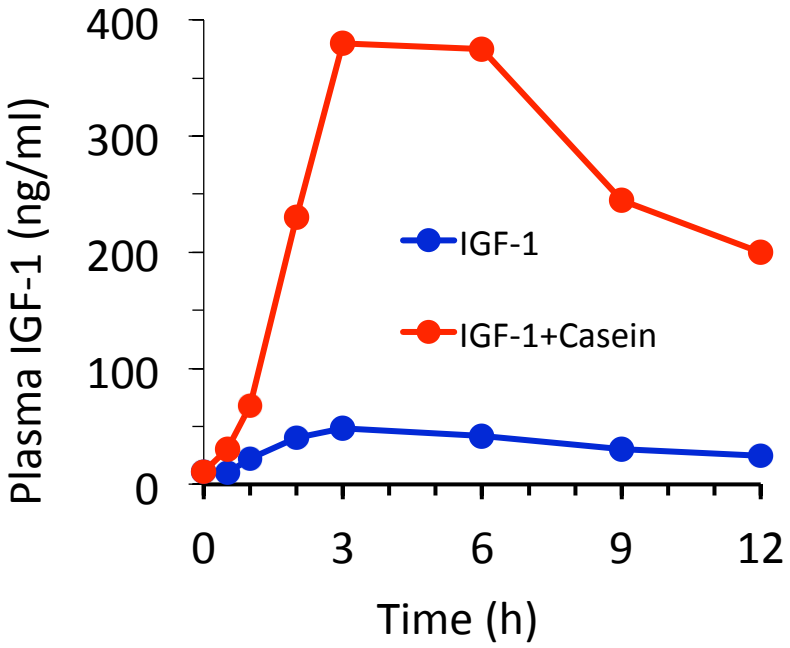
IGF-1 alone



IGF-1 + Casein

Intestinal Absorption of Milk IGF-1?

Kimura et al. 1997 - J Pharmacol Exp Therapeutics 283:611-618



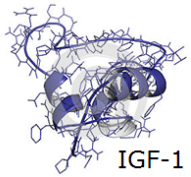
IGF-1
200 μg/ml

IGF-1 **Casein**
200 μg/ml **0.2 g/100 ml**

Intestinal Absorption of Milk IGF-1?

Kimura et al. 1997 - J Pharmacol Exp Therapeutics 283:611-618

200 μg/ml

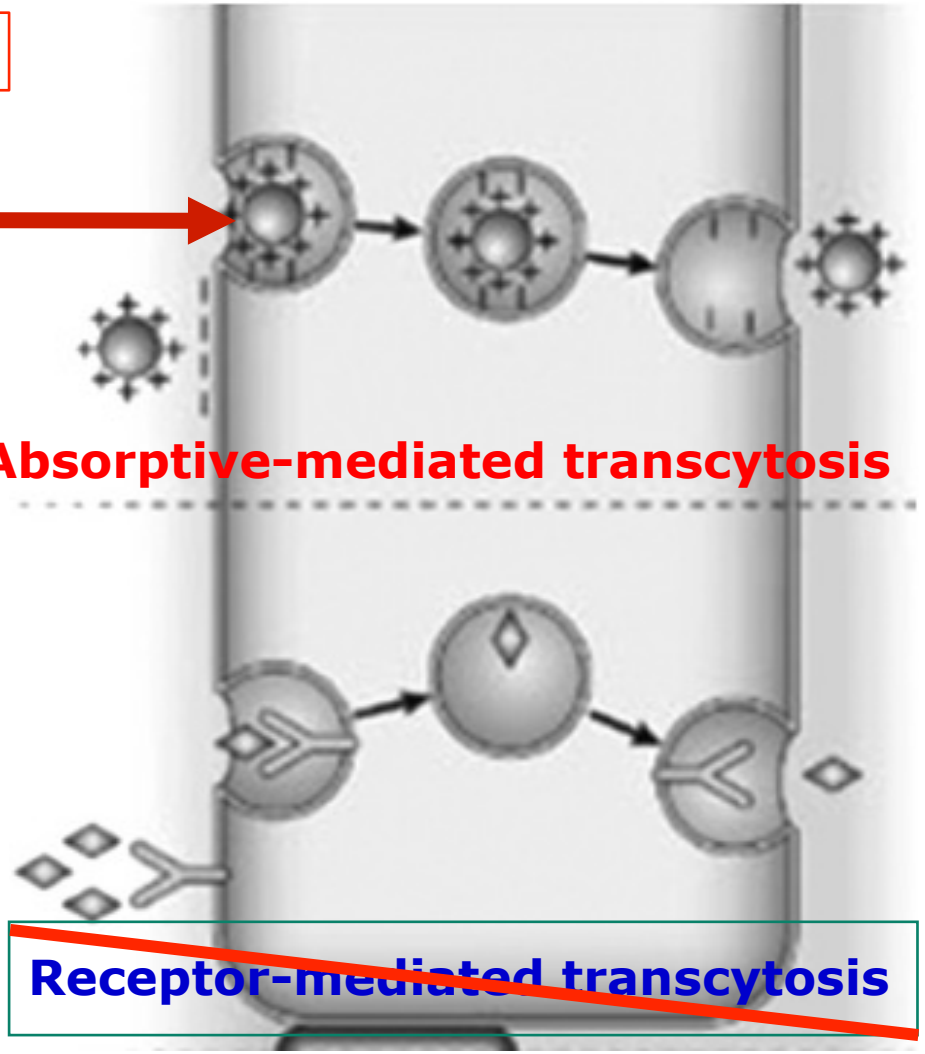


Keywords:

- escapes digestion in the stomach;
- poor absorption

BUT

- protective effect of casein
- local action



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Intestinal Absorption of Milk IGF-1?

Physiological conditions

- IGF-1 concentration in cow milk: **≈4 ng/ml**
- Casein concentration in cow milk: **2.8 g/100 ml**
- Casein **does not escape stomach digestion** and does not reach the small intestine intact

Experimental setting

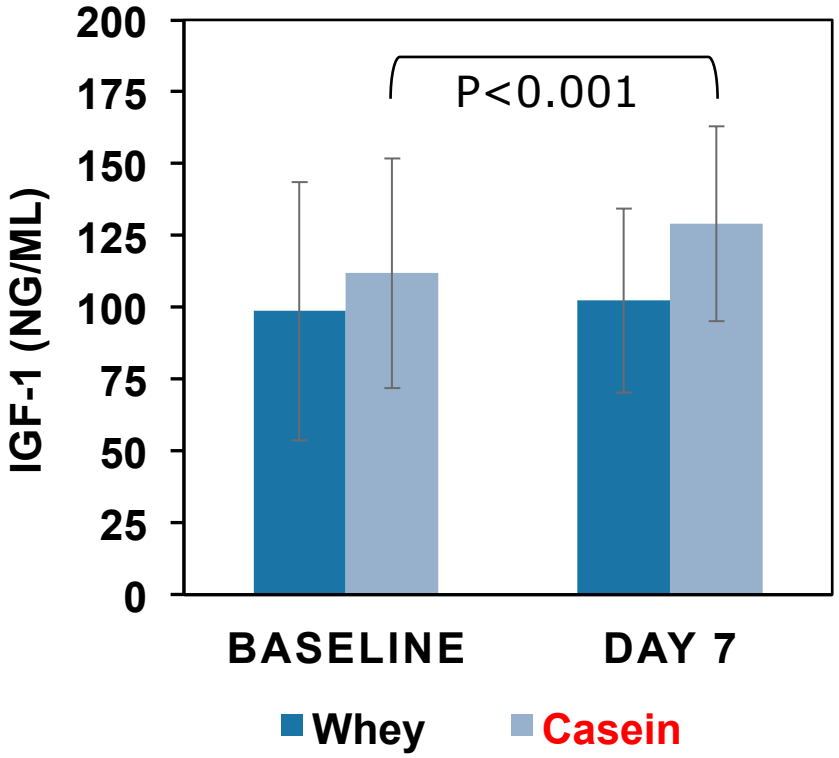
- IGF-1 concentration in saline: **200 μg/ml**
- Casein concentration in saline: **0.2 g/100 ml**
- Casein added **intact to the small intestine** environment

Kimura et al. 1997 - J Pharmacol Exp Therapeutics 283:611-618

Indirect effects of milk in stimulating endogenous IGF-1 release

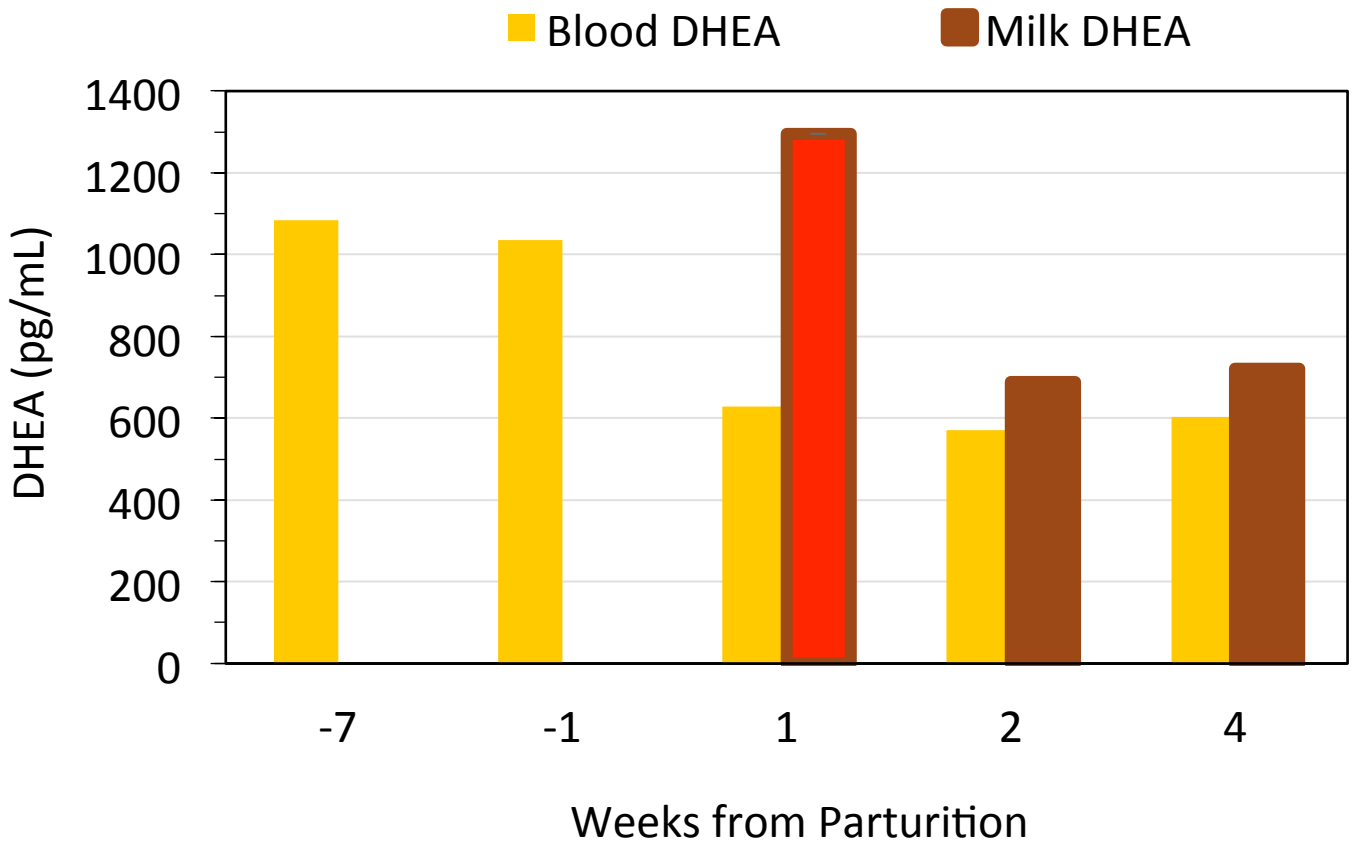
- 8-year-old boys (N=57)
- Eating their habitual diet
- **Problem**: most subjects drank milk (<500 ml/day)
- Supplemented with milk-based drinks:

In 540 ml/day	
Whey (g)	10.5
Casein (g)	42.0

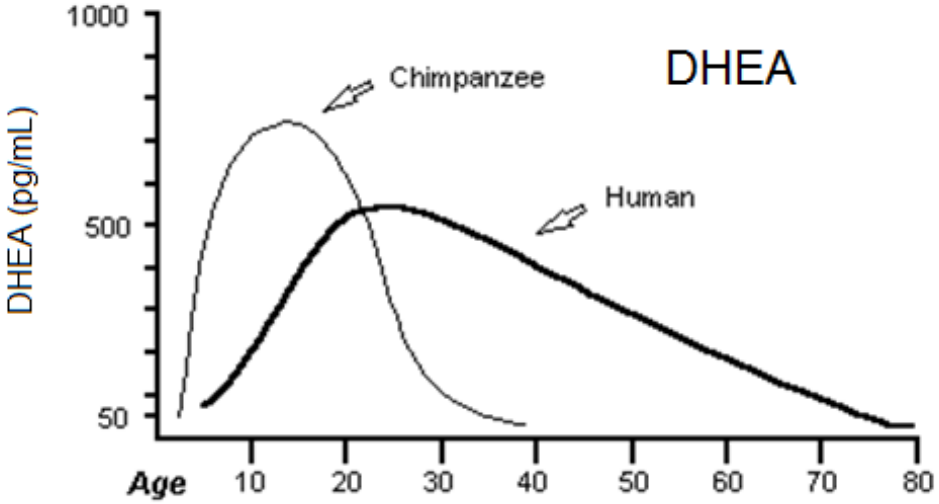


Hoppe et al., 2009 – Eur J Clin Nutr **63**, 1076-1083

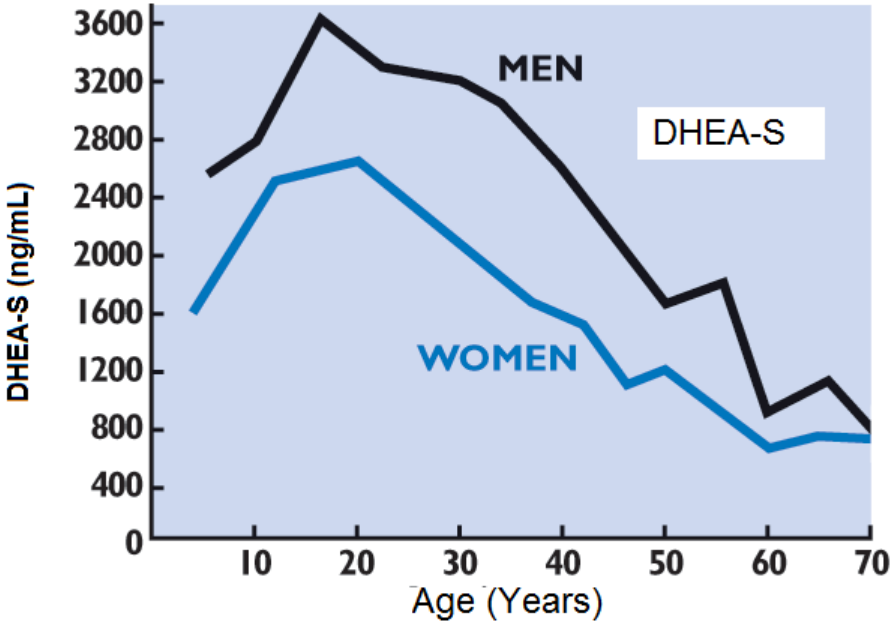
DHEA


Blood DHEA
Milk DHEA
DHEA (pg/mL)
1400
1200
1000
800
600
400
200
0
-7
-1
1
2
4
Weeks from Parturition

DHEA (androgen precursor)



DHEA-S in cow's plasma:
Same magnitude of DHEA



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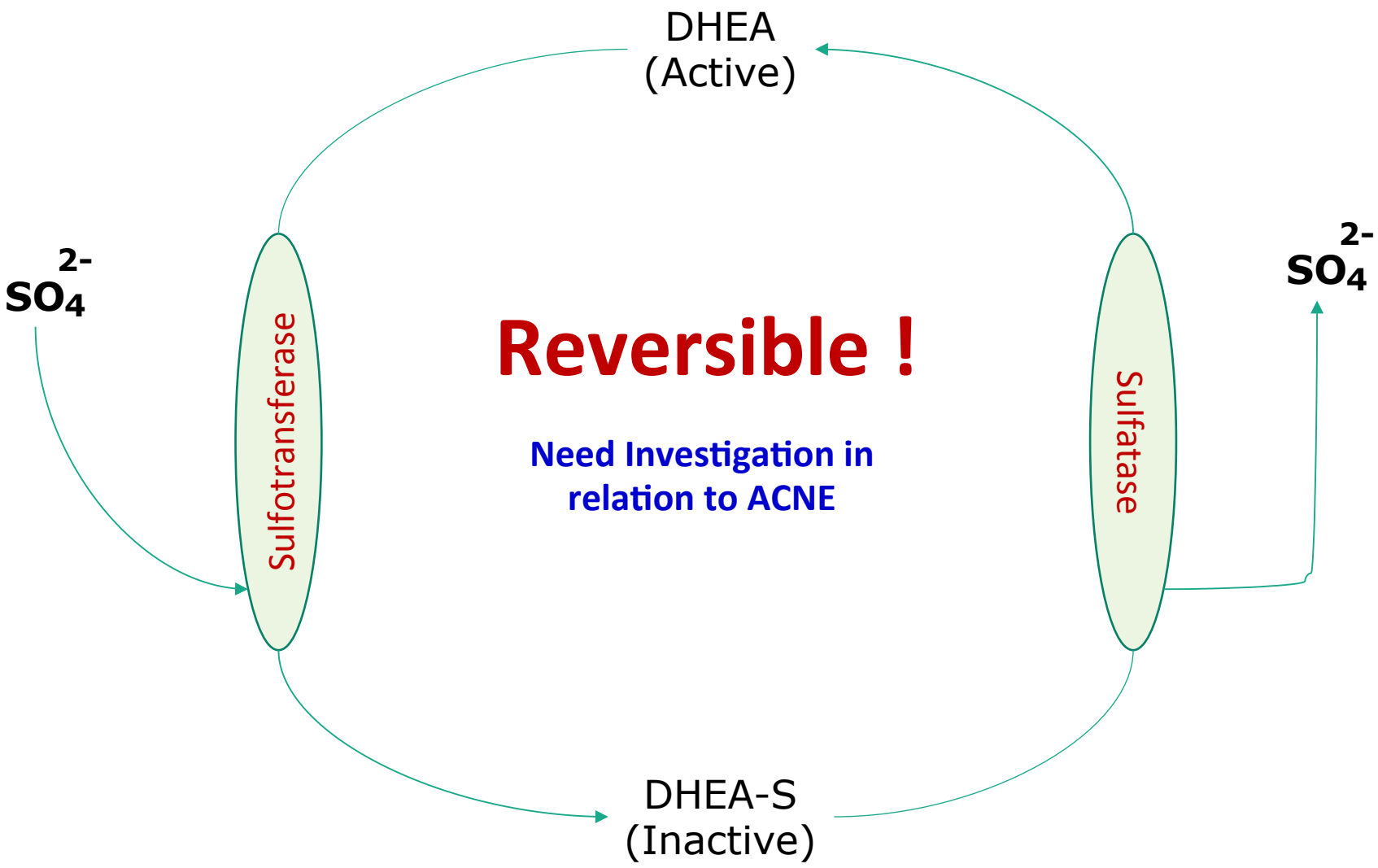
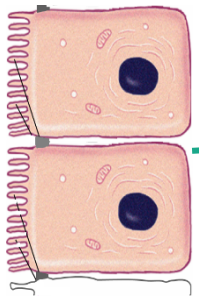
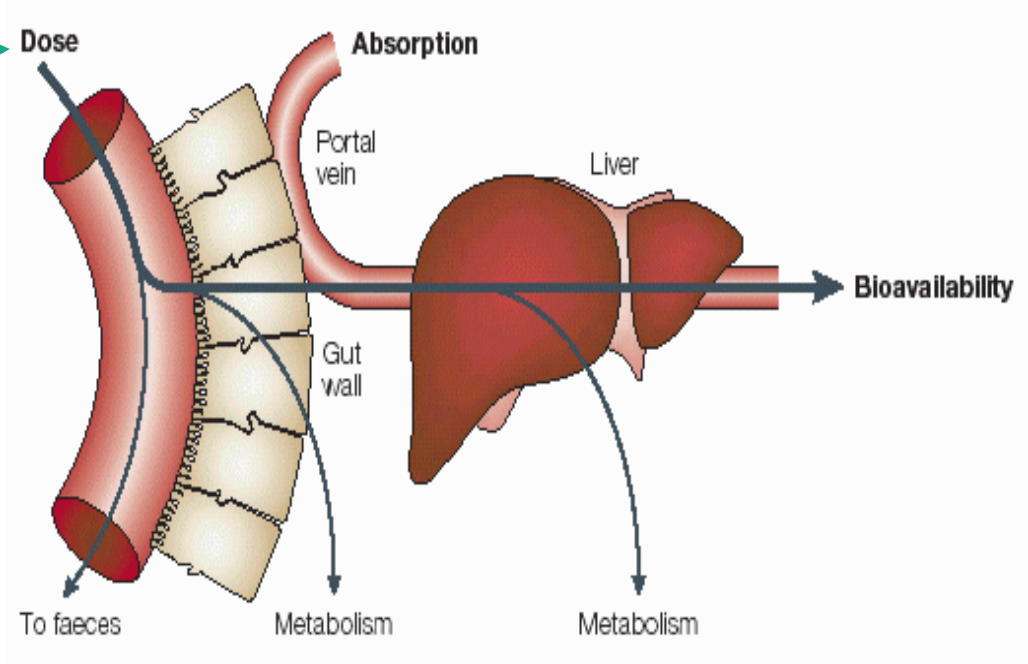
DHEA in human blood



Steroid Hormone
High concentrations





One CYP isoform

Many Substrates
(drugs/hormones)

CYP

Xenobiotic

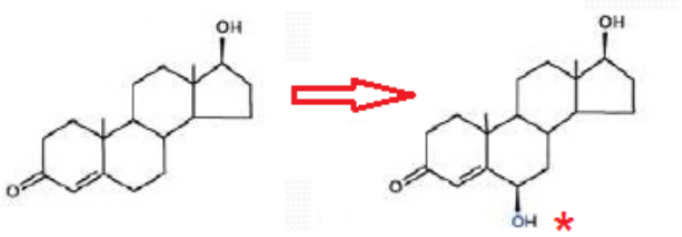
Phase I - Activation

Reactive intermediate

Phase II - Conjugation

Conjugate

Excretion

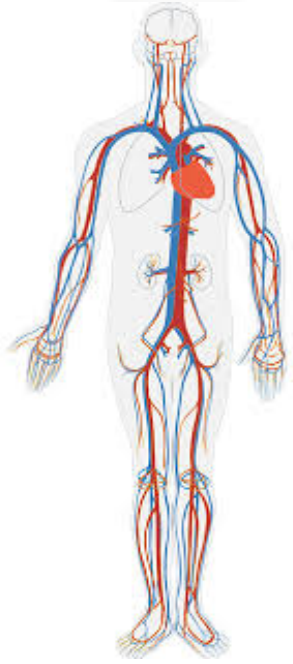


Testosterone 6β,OH-Testosterone

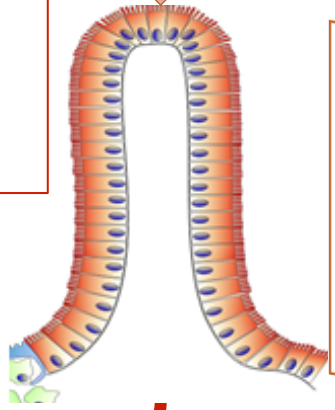
What we get in a glass of milk ?

100 mL

Hormone	Quantity
Oestradiol	40-110 pg
DHEA	80-100 ng
IGF-1	400-800 ng



Can a glass of milk affect circulating hormone concentrations?



Probably Not

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Esiste un «rischio ormonale» associato al consumo di latte?

Letteratura scientifica (talvolta, pseudoscientifica basata su conoscenze "aneddotiche") mette in dubbio l'utilità dell'assunzione di latte (rischio per la salute umana).

L'interazione tra l'alimento e il consumatore dovrebbe considerare ogni possibile contesto

e

Mettere in evidenza i meccanismi di interazione tra alimento e organismo.

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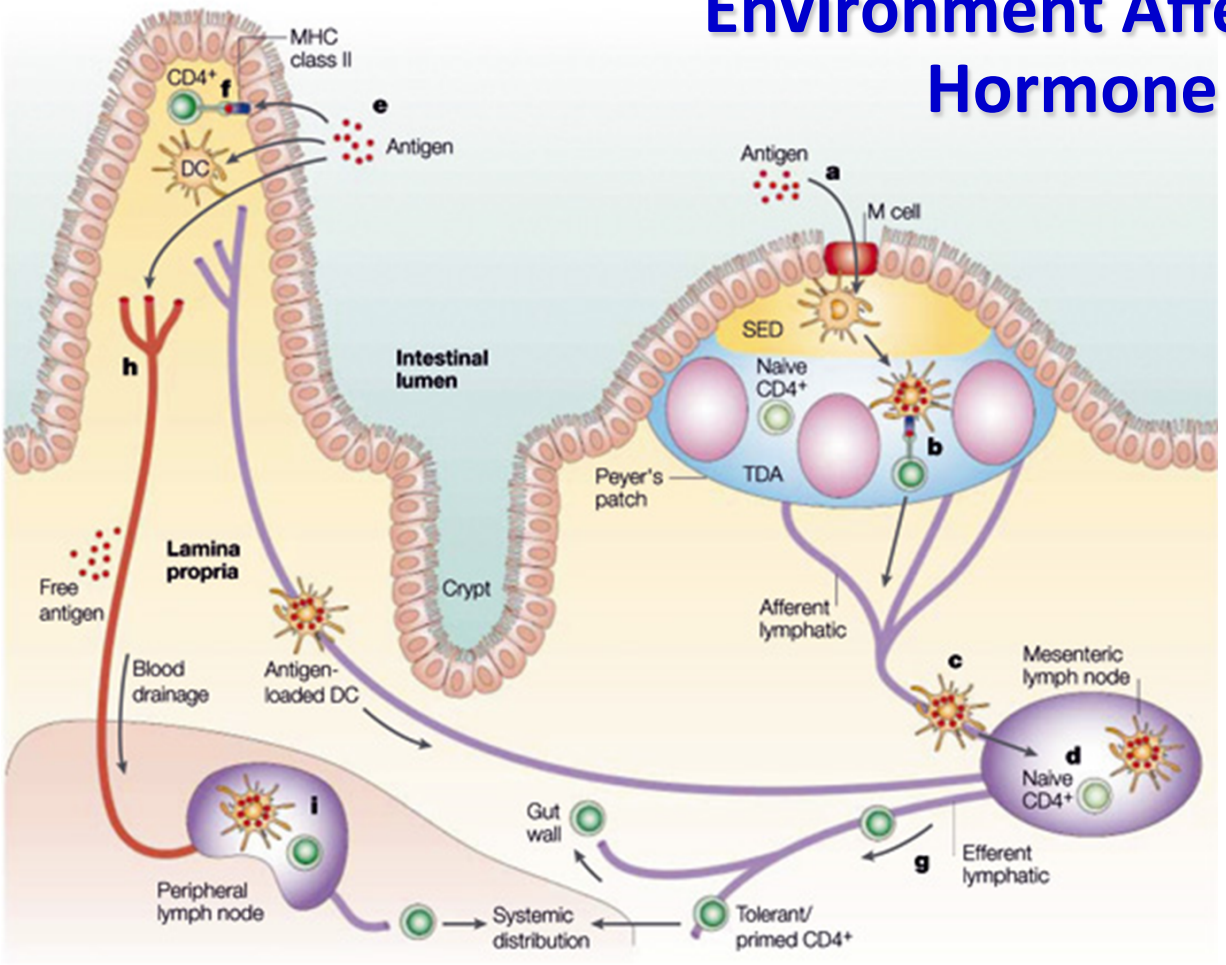
The Next Question:

(How) Can Disease/Intestinal Environment Affect Intestinal Hormone Absorption?



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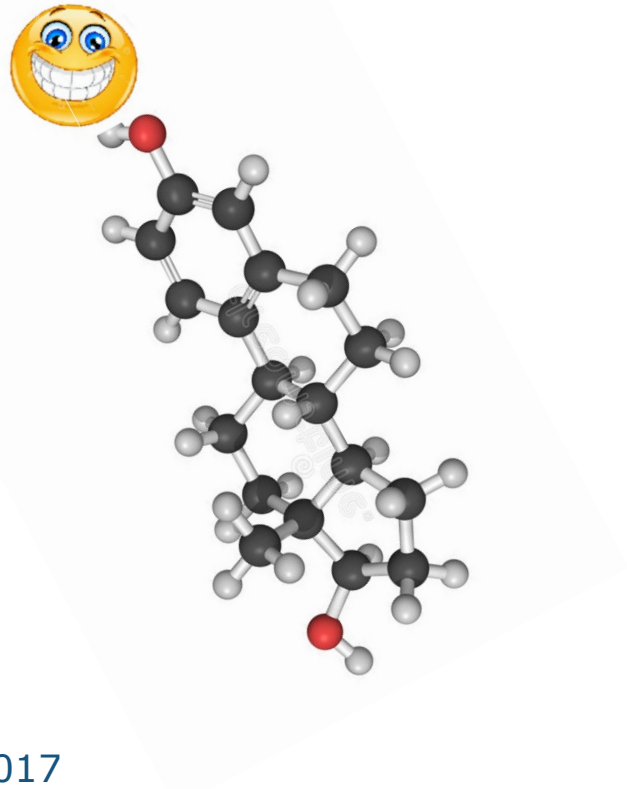
Grazie per l'attenzione



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