# DHEA:
# das unterschätzte Mutterhormon

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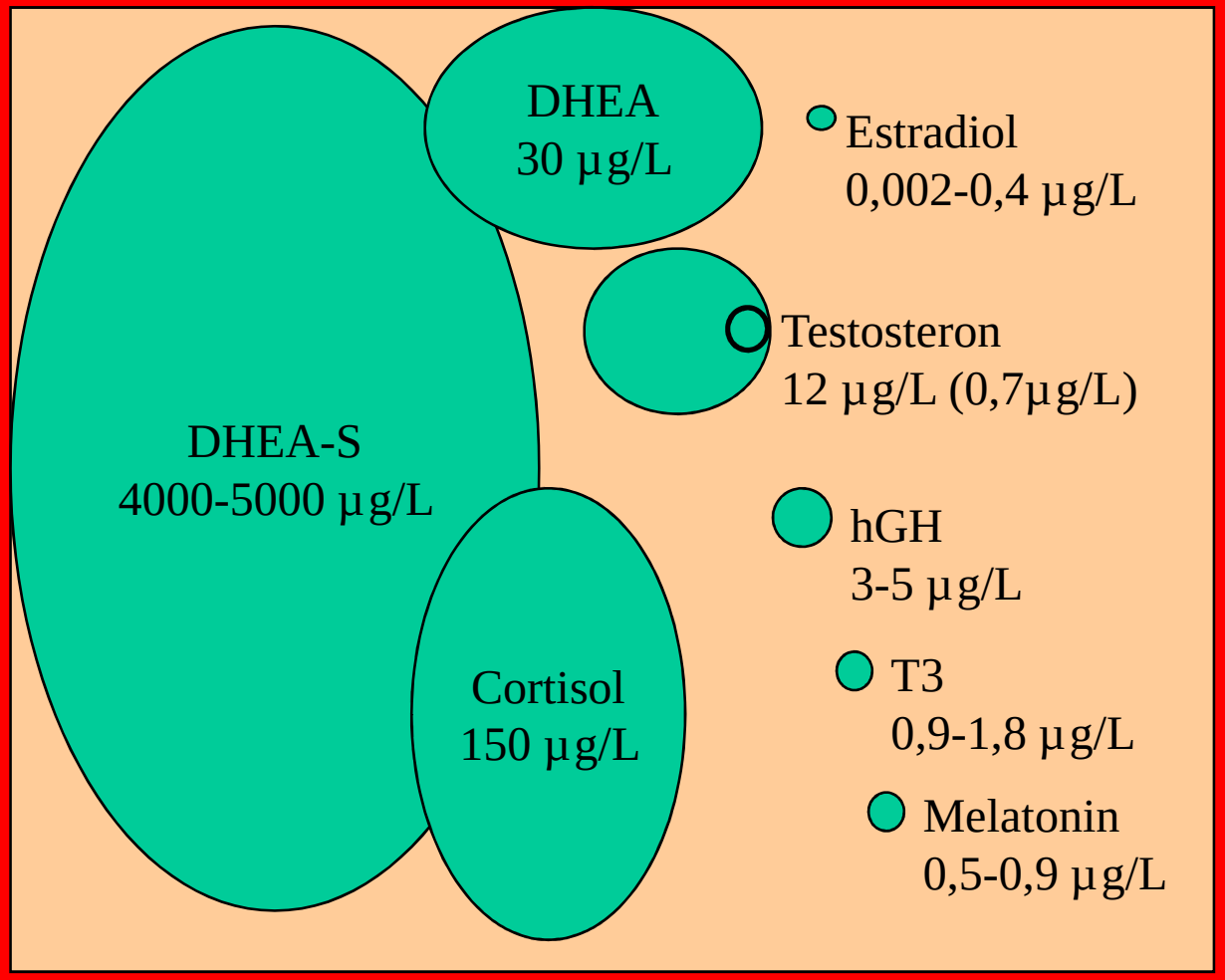
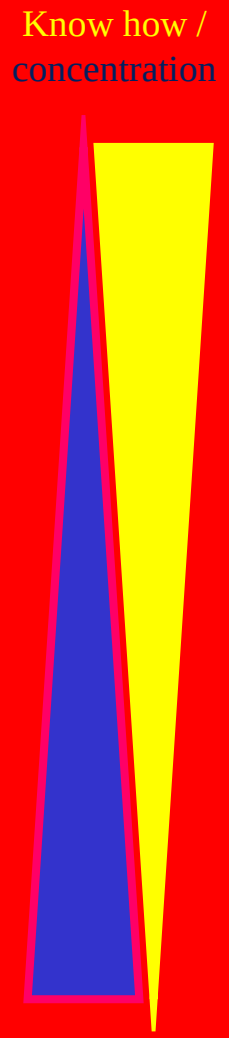
**Kalletal**

# Homone concentraion within our blood



**Topics:**

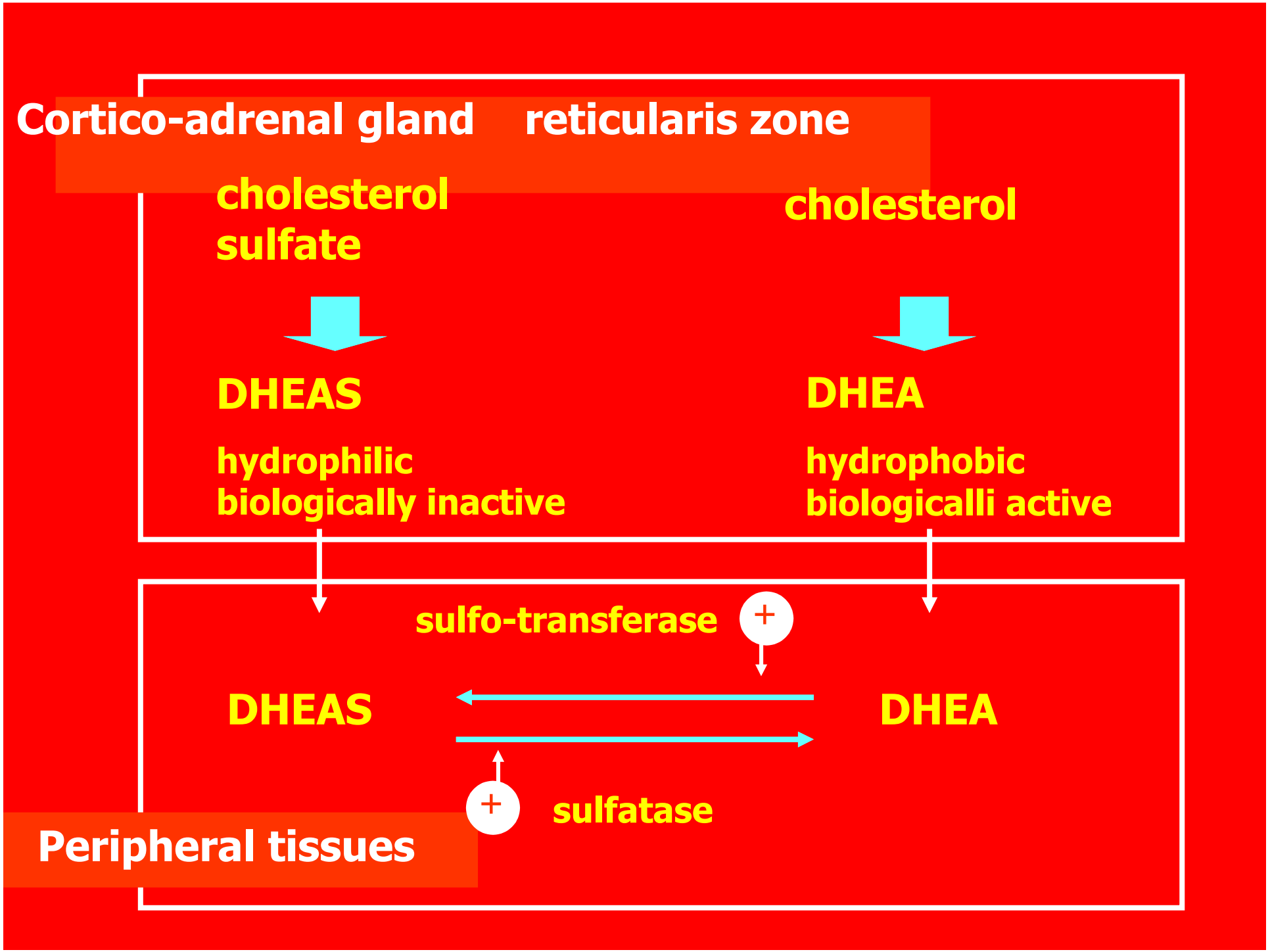
**a) the most important physiologic steps of DHEA secretion**

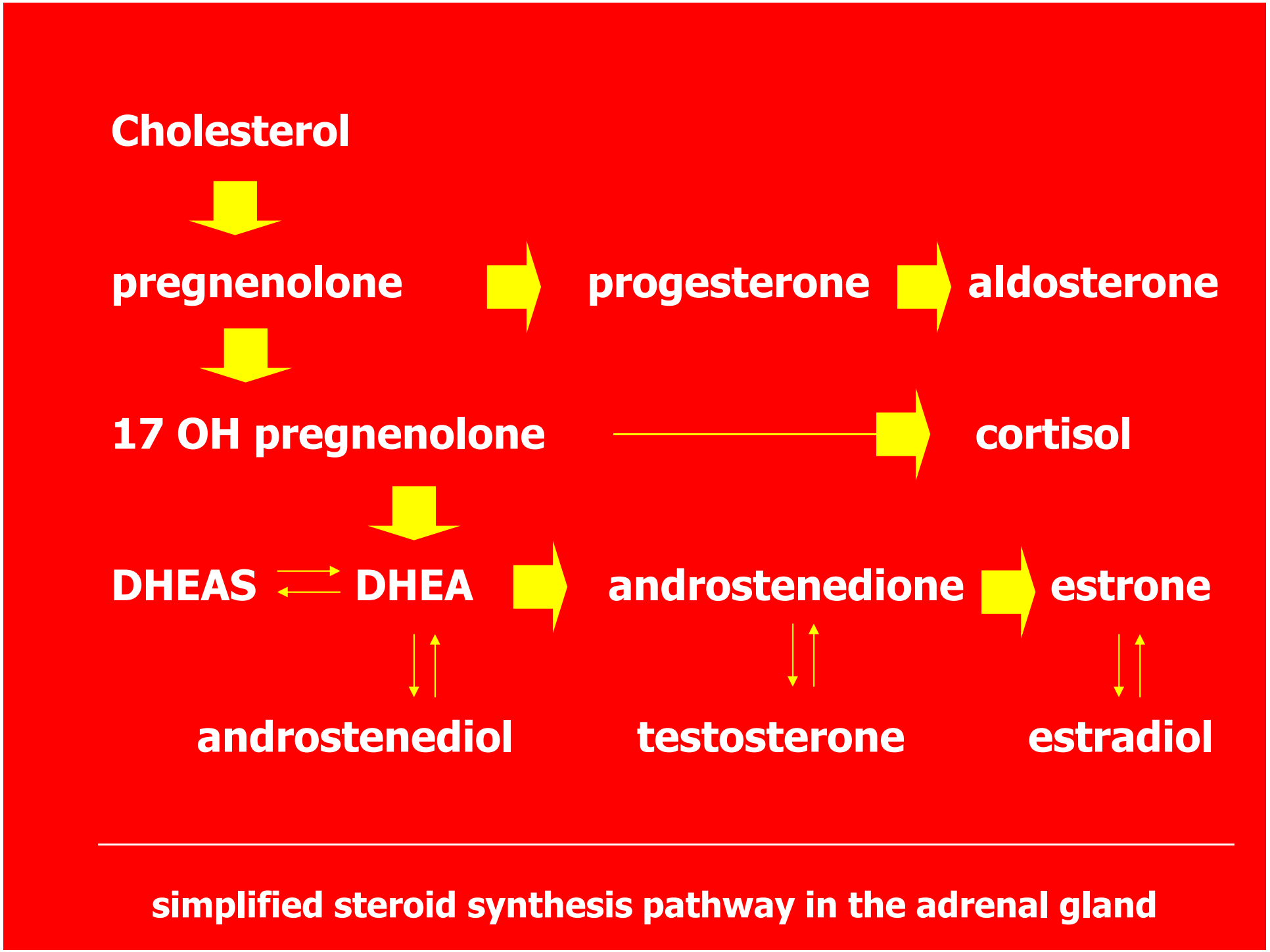
**b) mechanisms of action of DHEA**

**c) DHEA secretion modifications in aging (adrenopause)**

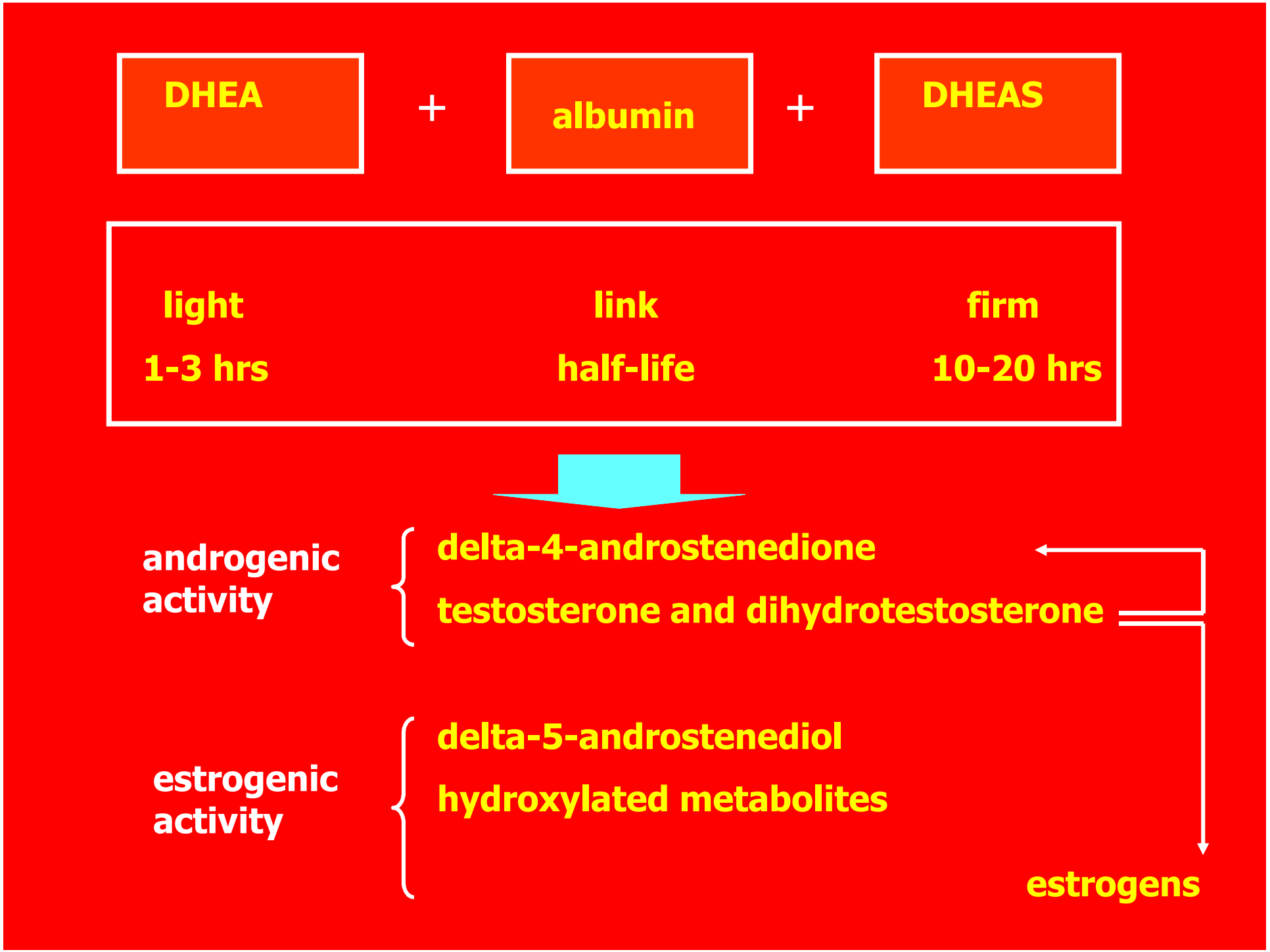
**d) potential clinical therapeutic implications**

**e) DHEA within the clinical pratice**


Cortico-adrenal gland reticularis zone
cholesterol sulfate
cholesterol
DHEAS
DHEA
hydrophilic biologically inactive
hydrophobic biologicalli active
sulfo-transferase
+
DHEAS
DHEA
+
sulfatase
Peripheral tissues




simplified steroid synthesis pathway in the adrenal gland


DHEA
+
albumin
+
DHEAS
light
1-3 hrs
link
half-life
firm
10-20 hrs
androgenic activity
delta-4-androstenedione
testosterone and dihydrotestosterone
estrogenic activity
delta-5-androstenediol
hydroxylated metabolites
estrogens

The synthesis from DHEA of the most potent androgens and estrogens involves several enzymes

- 3 beta and 17 beta hydroxysteroid dehydrogenases
- delta 5 delta 4 isomerases
- 5 alfa reductase
- aromatases

Such enzymatic activity is widely distributed in many peripheral tissues:

adipose tissue,bone, muscle, breast, prostate, skin, brain, liver (intracrinology)

# DHEA/DHEAS peripheral bioconversion

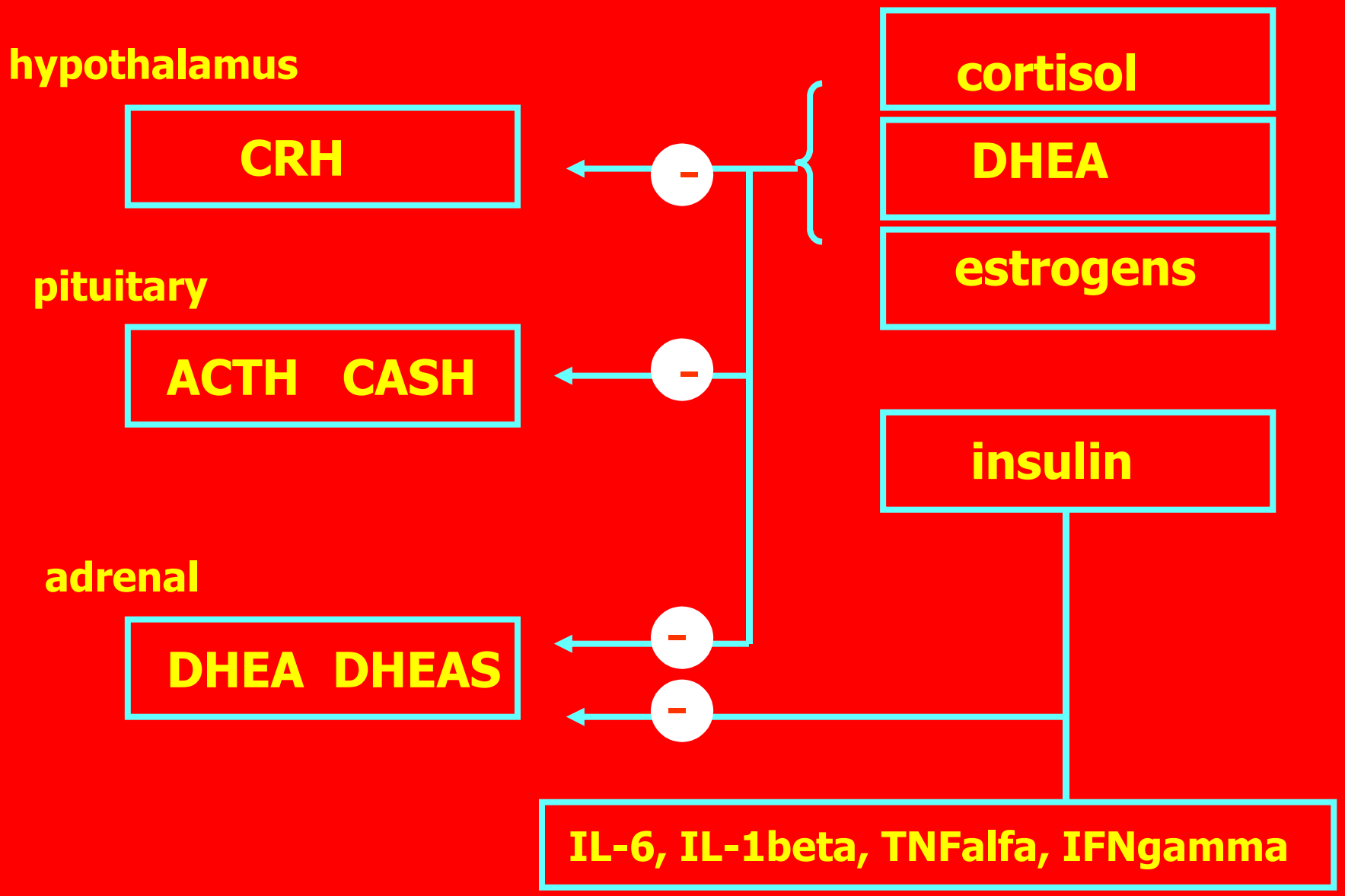
in adipose tissue, bone, muscle, breast, prostate, skin, brain and particularly liver

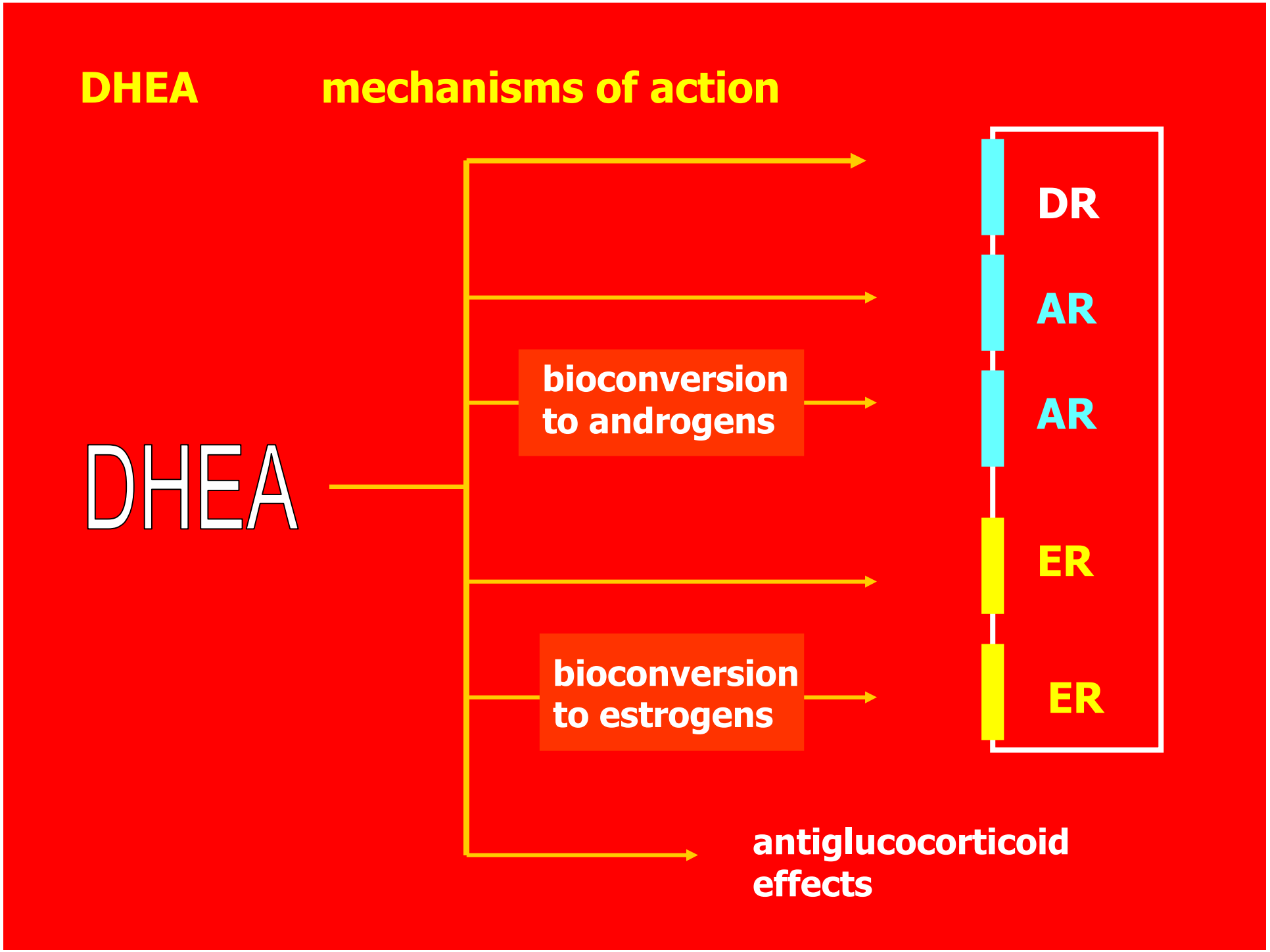
produces

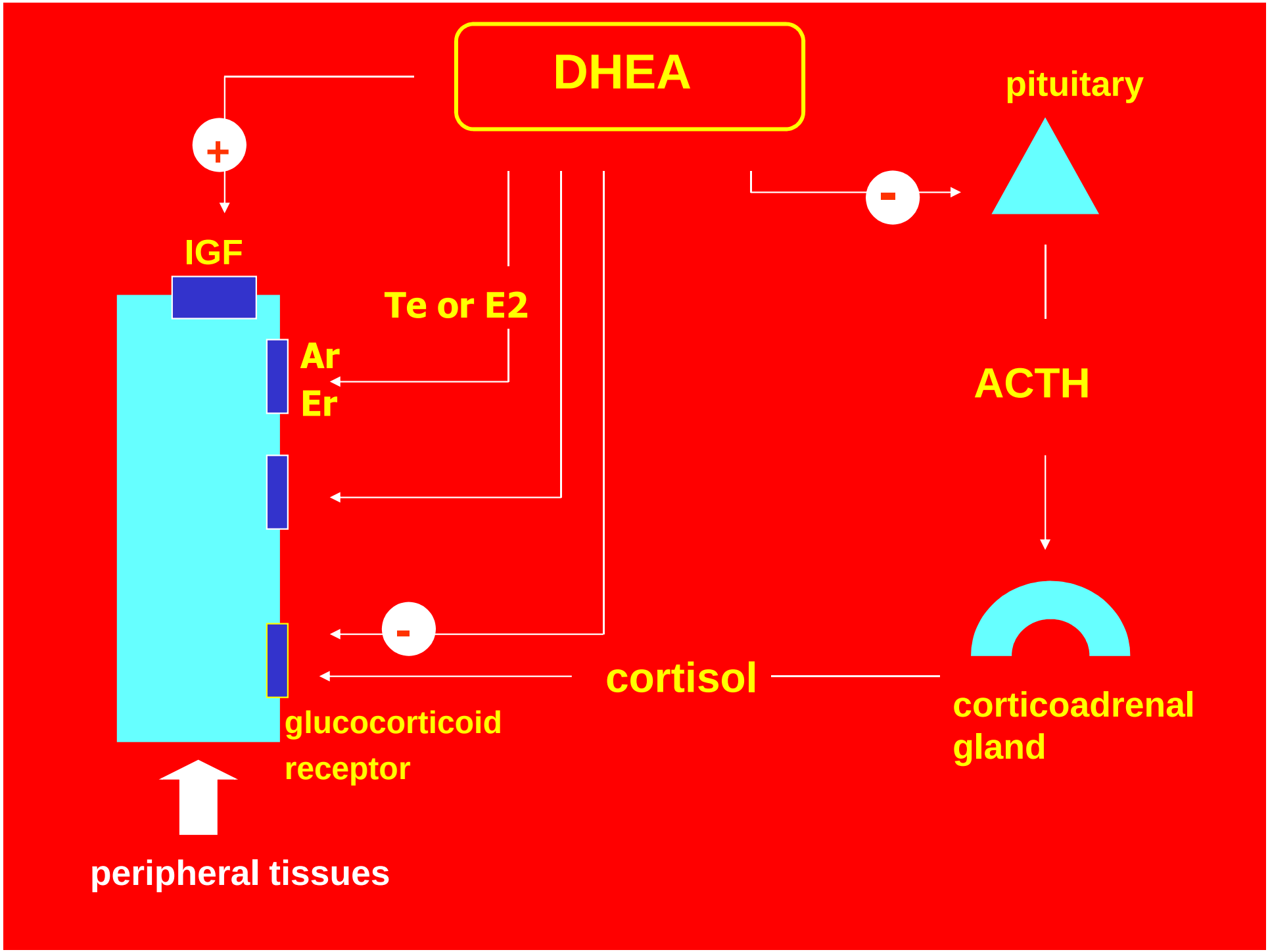
30% of total androgens in men

90% of estrogens in post-menopausal women

# DHEA/DHEAS control secretion mechanisms

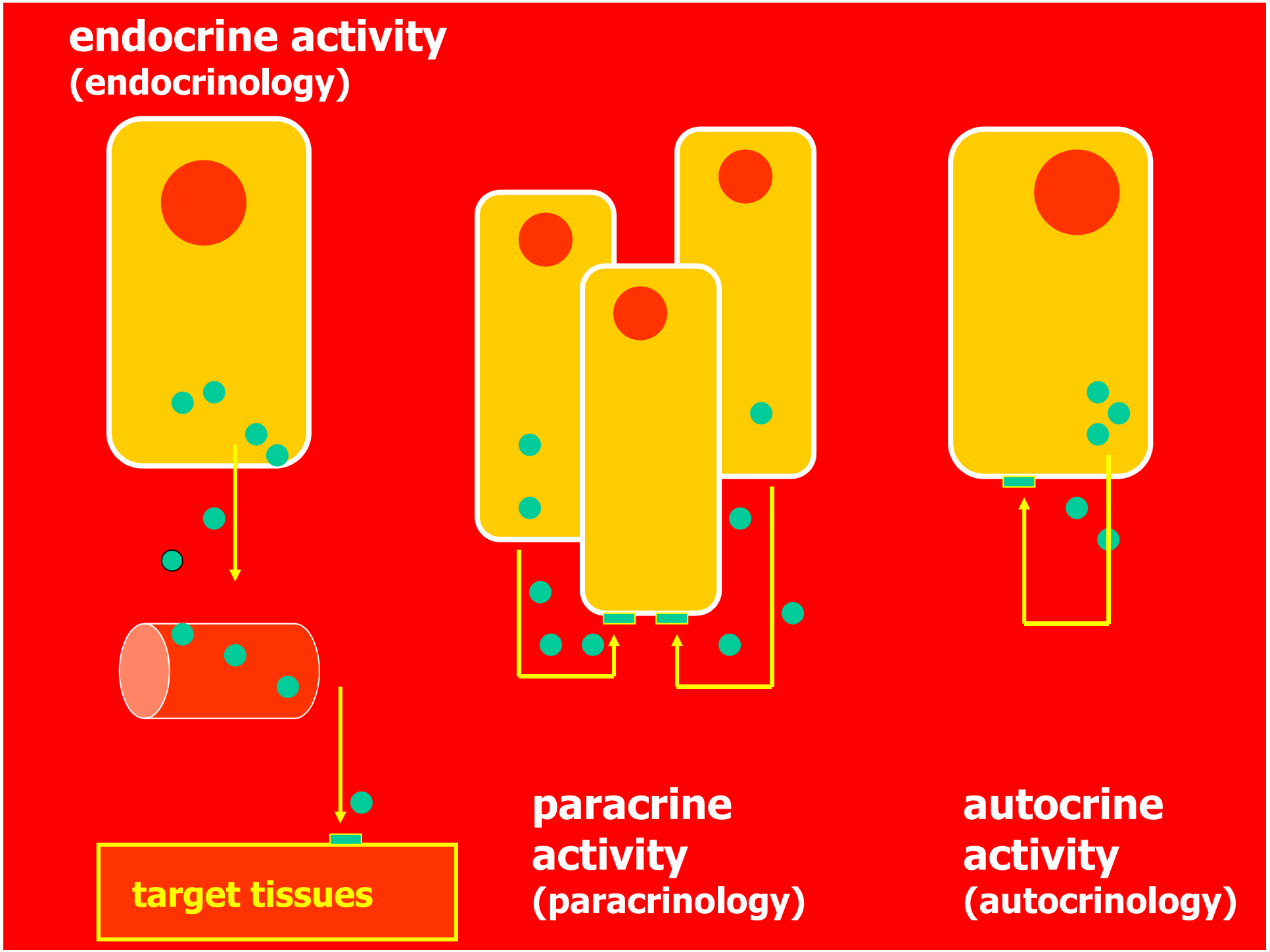



DHEA
mechanisms of action
DHEA
bioconversion
to androgens
bioconversion
to estrogens
antiglucocorticoid
effects
DR
AR
AR
ER
ER

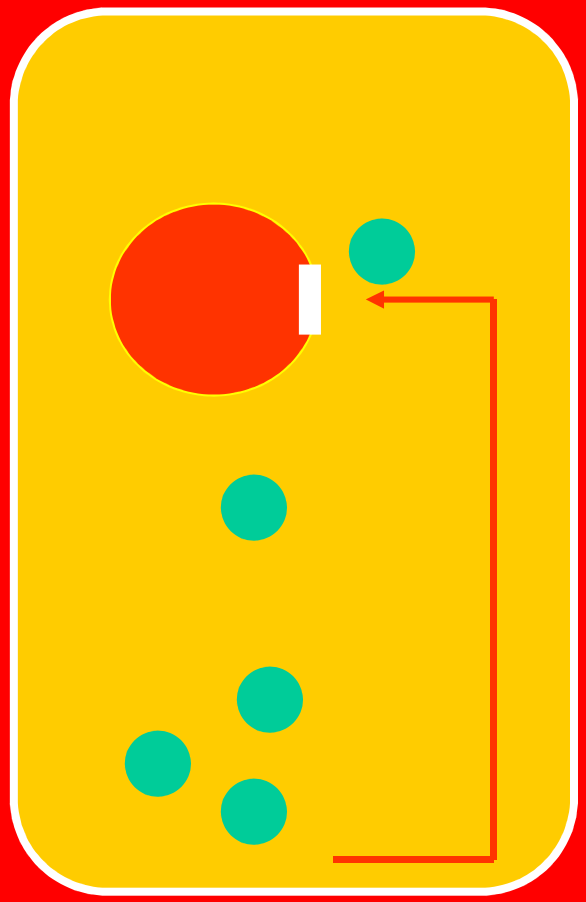

DHEA
pituitary
+
-
IGF
Te or E2
Ar
Er
ACTH
-
cortisol
glucocorticoid
receptor
corticoadrenal
gland
peripheral tissues

## DHEA specific binding sites

- **Cytosolic binding sites (protein kinase activity)**
  - **mouse melanoma cells**
  - **murine T cells, T cells hybridoma**
  - **human lymphoid cell line and in monocytes**
- **Membrane binding sites (G proteins and eNOS)**
  - **bovine aortic endothelial cells**
  - **human vascular smooth muscle cells**

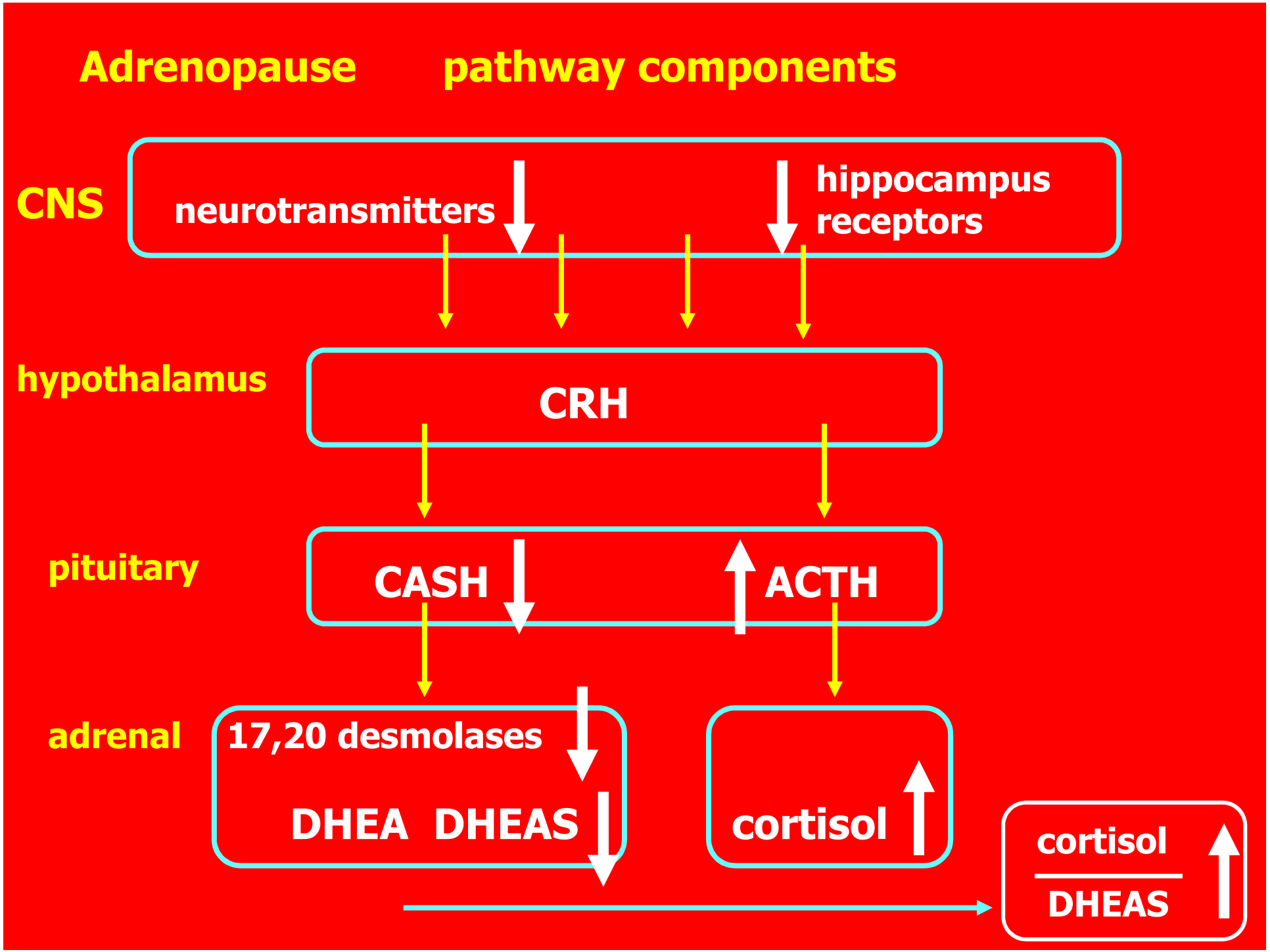

endocrine activity
(endocrinology)
target tissues
paracrine
activity
(paracrinology)
autocrine
activity
(autocrinology)

# intracrine activity



active hormones exert their action in the same cells where synthesis take place without release into the pericellular compartment

**intracrinology (Labrie)**


Adrenopause pathway components
CNS
neurotransmitters
hippocampus receptors
hypothalamus
CRH
pituitary
CASH
ACTH
adrenal
17,20 desmolases
DHEA DHEAS
cortisol
cortisol
DHEAS

**In CHIANTI study**

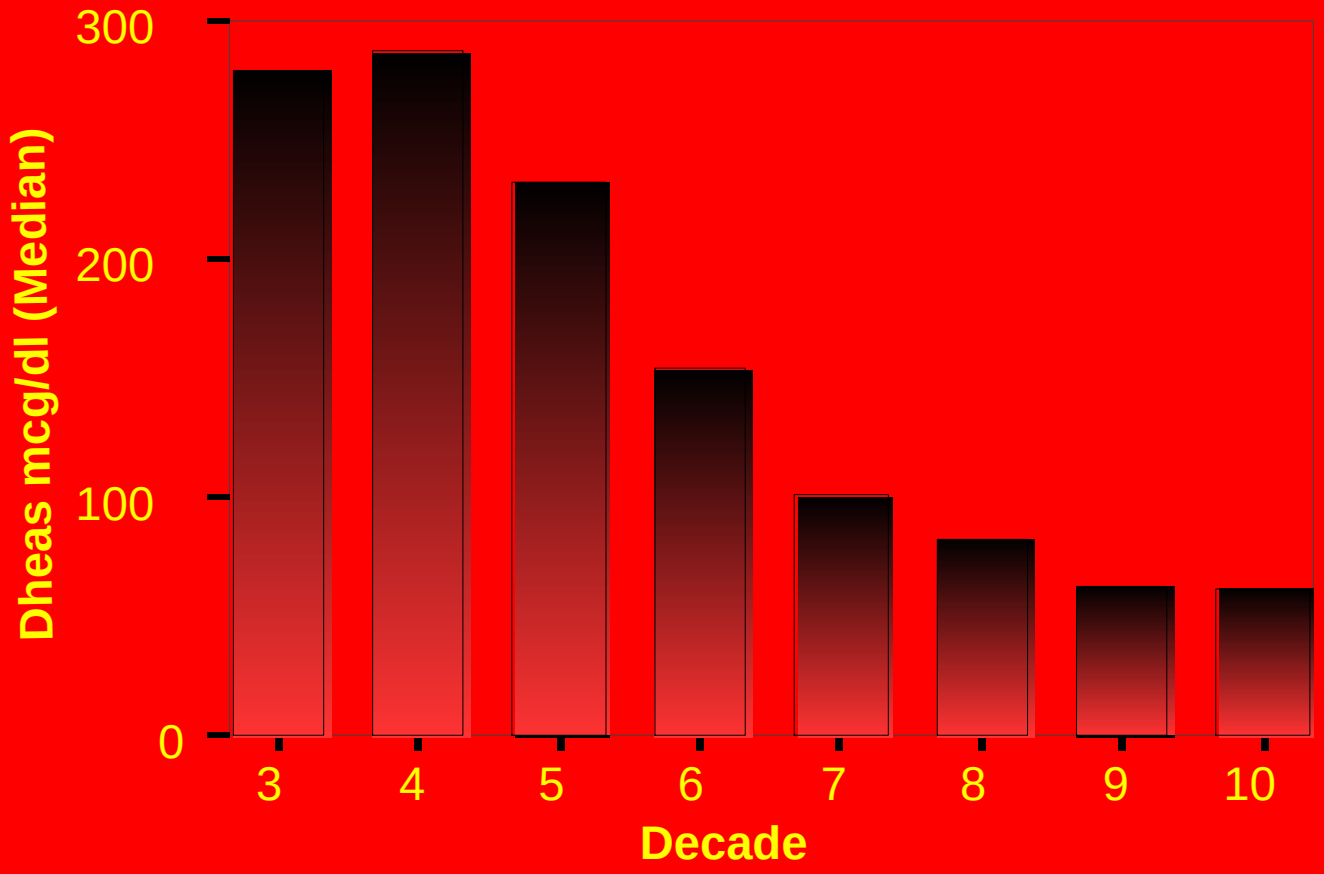
**# population based study of persons living in CHIANTI geographic area (Tuscany Italy)**

**# 1453 persons (age 20-102 years) 587 males and 866 females, selected using a multistage sampling method**


**Ferrucci et al JAGS 48:1618-1625,2000**

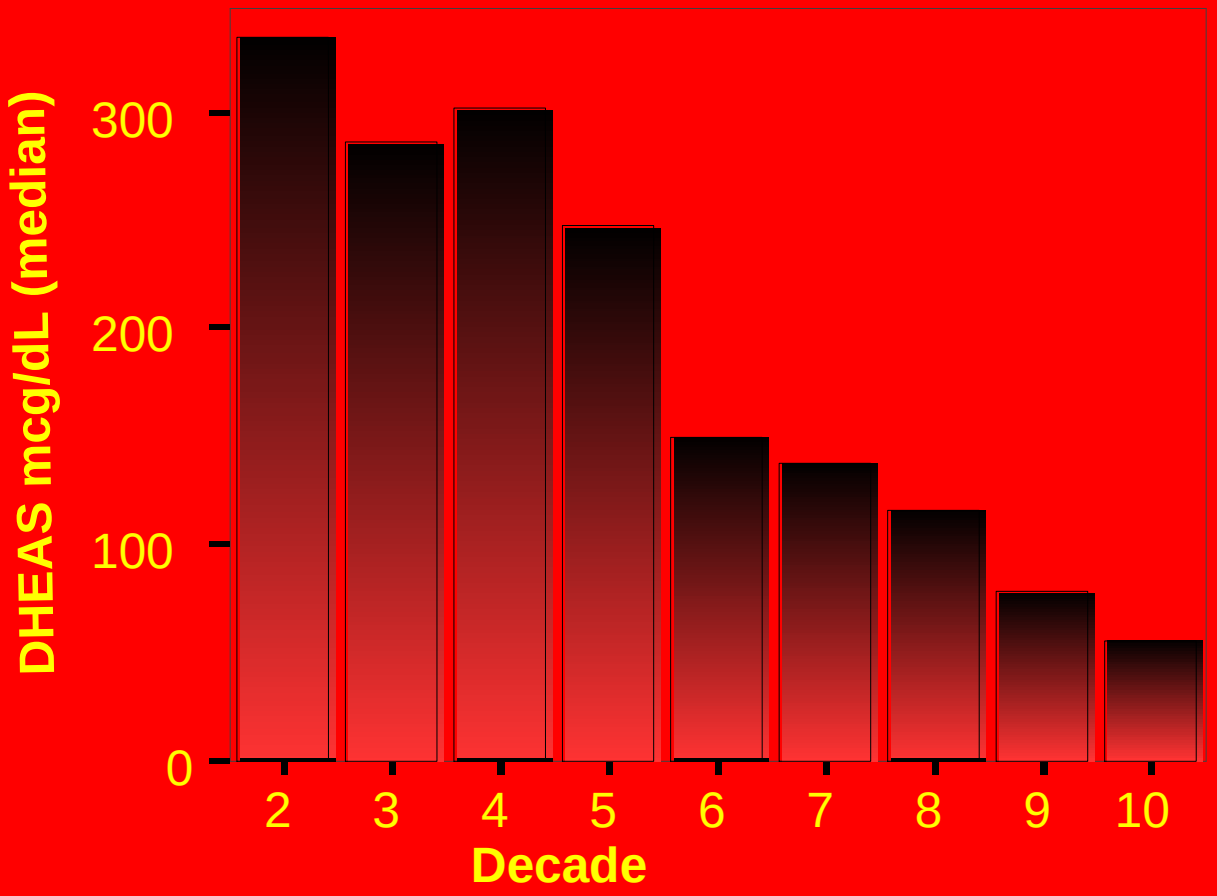
**Valenti et al J Gerontology Med Sc, 59A:466-472,2004**

LogDHEAS= 6.63-0.03*age P 0.000 R2 0.29




Female group inChianti study

LogDHEAS= 2.76-0.001*age  P 0.000  R2 0.50




Male group  inChianti study

## DHEAS and body composition (fat mass and muscle mass and strength)

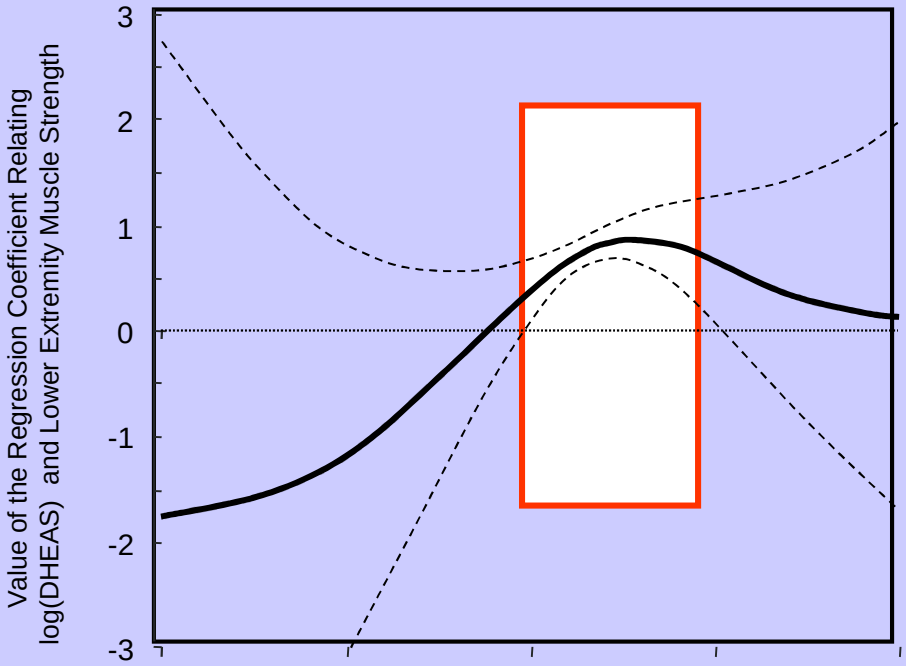
**Fat mass** **Observational studies**

Association
- negative (De Pergola et al Metabolism 1991; Wild et al AmJ Obs Gyn 1983)
- positive (Mazza et al JEI 1999; Abbasi et al JAGS 1998)
- insignificant (Barrett-Connor et al JCEM1996; Denti etal Metabolism 1997)

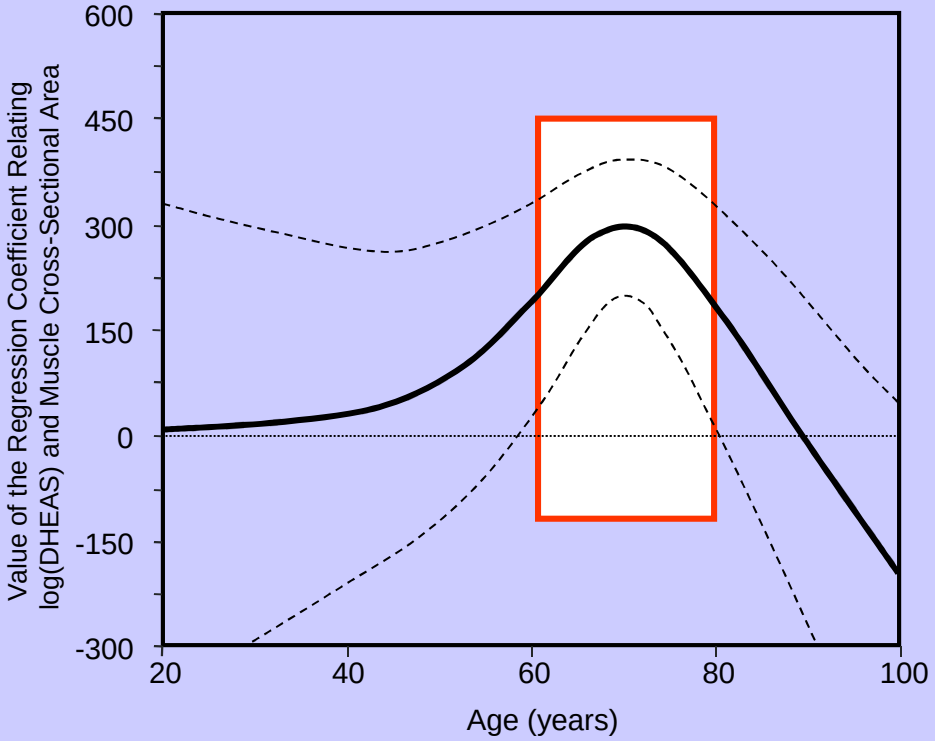
**Muscle mass and strength** **Observational studies**

Association
- positive (Kostka et al Eur J Ap Physiol 2000; Valenti et al J Gerontol 2004)

**muscle strength**




**muscle mass**




**Valenti G et al. J Gerontol Med Sc**

**2004, 59A,5,466-472**

## DHEAS and body composition (Fat mass and muscle mass and strength)

### Intervention studies

Only 12 RCTs considering the effect of DHEA on body composition and muscle strength are available

- in 4 of them → decrease in total fat mass only in men, in abdominal fat in both women and men (Morales,1998, Villareal, 2004, Gomez-Santos, 2011)

- in 2 of them → increase in muscle mass and strength in women and in men (Villareal,2004; Kenny, 2010)

→ Strength of evidence Ib

## DHEA and bone metabolism

### Observational studies

- specific binding sites in human osteoblastic cells (Kasperk et al, Cal Tissue Int 1997)

- positive association of DHEAS with BMD in cross-sectional studies (Wild et al ProcSoc Exp Biol Med 1987; Nawata et al Mech Ageing Dev 2002; Nordin et al JCEM, 2012)

- not confirmed in prospective studies (Barrett-Connor et al Am J Epidemiol 1993)

## DHEA and bone metabolism

### Intervention studies

**Only 5 RCTs considering the effect of DHEA on BMD and bone metabolism are available**

**- in three of them and mostly in women and less in men**

**→ increase in BMD (Christiansen 2011)**

**→ decrease in one marker of bone resorption (CTx) (Baulieu et al Proc Natl Acad Sci 2000)**

**→ normalisation of bone density in corticoide treatment (Papierska 2012)**

**→ Strength of evidence Ib**

## DHEA and lipoprotein metabolism

### Observational studies

- contradictory results in Total,LDL,HDLCholesterol levels frequently with different behaviour between men and women

(Barrett-Connor et al Circulation 1995; Barrett-Connor et al AnnNY Acad Sci 1995; Barrett-Connor et al Ann Int Med 1992; Hautanen et al J Steroid Bioch Mol Biol 1994; Kiechl et al Art Thromb Vasc Biol 2000)

## DHEA and lipoprotein metabolism

### Intervention studies

7 RCTs considering the effect of DHEA on lipid parameters are available

- in one of them → decrease of totral Chol and HDL-C in men (Artl et al JCEM 2001)

- in 4 of them → slight decrease of HDL-C in women (Morales et al JCEM 1994; Morales et al Clin Endocrinol 1998;Casson et al Fert Steril 1998; Gomez-Santos, 2011)

- in one of them → decrease of LDL-C and Triglycerides (Lasco et al Eur J Endocrinol 2002)

→ No clear evidence of effect up today

DHEA replacement may either improve or worsen plasma lipid pattern perhaps in relation to sex and individual sensitivity

## DHEA and glucose metabolism

### Observational studies

- most of them show no association between DHEA and DHEAS with glucose and insulin blood levels in basal conditions and after OGTT (Haffner et al Diabetes 1994; Haffner et al Diabetes 1995; Denti et al 1997; Maccario et al Clin Endocrinol 1999)

- however in women and particularly in men an inverse association between DHEAS and fasting glucose and insulin levels has been found (Haffner et al Metabolism 1994; Paolisso et al Metabolism 1997)

## DHEA and glucose metabolism

### Intervention studies

9 RCTs considering the effect of DHEA on glucose metabolism are available

in one study → decrease in insulin response to OGTT

→ increase in insulin sensitivity index

in both men and women (Villareal et al JAMA 2004)

in three study → increase in insulin sensitivity (euglycemic clamp) mostly in women

( Lasco 2001, Talaei, 2010, Jankowski, 2011)

→ strength of evidence Ib

# DHEA and cardiovascular system

## Observational studies (1)

- cross-sectional and prospective studies show inverse association of DHEAS with cardiovascular events ad cardiovascular mortality in men (Barrett-Connor et al Circulation 1988; LaCroix et al Circulation 1992)

- positive association of DHEAS with cardiovascular mortality in post menopausal women (Barrett-Connor et al N Engl J Med 1987)

- higher DHEAS levels in male myocardial infarction survivors (Slowinska-Srzednicka et al Atherosclerosis 1989; Mitchell et al Circulation 1994)

- association of low DHEAS levels and the extent of atherosclerotic involvement of coronary arterie in men (Herrington et al J Am Coll Cardiol 1990)

## DHEAS and cardiovascular system

### Observational studies (2)

- positive relationship of DHEAS with BP especially in women; data less consistent in men with some reports excluding any association (Haffner et al Am J Epidemiol 1995; Mantzoros et al Am J Hypert 1995; Khaw et al N Engl J Med 1988; Schunkert et al J Hypert 1999; Bama et al Am J Hypert 1998; Hakala et al Eur Heart J 1998, Boxer, 2010)

- in vitro and in vivo demonstration of inhibition of human platelet aggregation

As a whole these reports might suggest that in older men and women DHEA supplementation may have a positive effect in term of cardiovascular disease prevention. No consistent intervention study (RCT) is available till now

## DHEA and CNS function

### Animal studies

**- observational studies**

DHEAS has been identified in the brain where it exibits local metabolism also in adrenectomised animals (Kishimoto 1972; Baulieu 1991)

**- intervention studies**

Effects on cortico-thalamic projection growth in embryo (Compagnone 1998)

Antagonism with GABA receptors (Majewska 1990)

Binding to NMDA receptors (Dermirgoren 1991)

Stimulation of serotonin synthesis (Abadie 1995)

Attenuation of neurotoxic effect of glucocorticoid exposure in hippocampal coltures (Kimonides 1999)

Reduction of cognitive decline in experimental Alzheimer dementia (Maurice 1998)

## DHEA and CNS function

### Human observational studies

- DHEAS has been found detectable in CSF with no (Ceresini 1997) or with slight significant correlation (Rudman 1997)
- Inverse correlation between DHEAS and presence of "organic brain syndrome" (Rudman 1990)
- low levels of DHEAS in patients with AD ( Swenderland 1989; Nasman 1991) not confirmed by others (Spat-Schwalbe 1990; Leblhinber 1990; Schneider 1992)

### Human intervention studies

- mood improvment after DHEA treatment in patients with depression (Wolkowitz 1999), dysthymia (Bloch 1999), anorexia (Gordon 2002)

## DHEA and CNS function

**6 RCTs considering the effect of DHEA on mood, well-beeing and libido in older persons**

→ No significant change, although a trend toward an increase of quality of life and mood especially in women (Morales 1994; Wolf 1997, Williams 2012)

**6 RCTs considering the effect of DHEA on cognition in older persons**

→ No improvement in cognition processes; only two study demonstrated an improvement in cognitive performance after stress or aging (Wolf, 1998, Ritsner, 2012)

→ No significant report comproving an improvement of well-beeing, mood and cognition in the elderly. However the trend toward improvement in women and the beneficial effects in younger patients with mood disturbances suggest potential benefits in more specific pathological conditions.

## DHEA and immunocompetence

**Animals studies**

**DHEA protects from polymicrobial sepsis and from endotoxic shock (Oberbek et al Crit Care Med 2001; Danenberg et al Antimicr Agents Chemoter 1992) and enhances cytokine production in T cells (Daynes 1992)**

## DHEA and immunocompetence

### Human observational studies

- Association of accelerated DHEA decline with HIV infections and septic shock and low DHEA levels are predictive of progressionof AIDS (Mulder 1992)

- Negative association of DHEA levels with IL-6 and lower DHEAS levels in  non survivors of septic shock (Beishuizen 2002)

- Negative correlation of DHEAS with neopterin (Ledochowski 2001)

- DHEAS reduced levels in inflammatory diseases (rheumatoid arthritis, SLE, ulcerative colitis and polymialgia rheumatica (Schwartz 2002; Straub 2000, Williams 2012)

## DHEA andimmunocompetence

**Human intervention uncontrolled studies**

- DHEA → decrease of T helper cells

→ inhibition of IL-6 (Casson 1993)

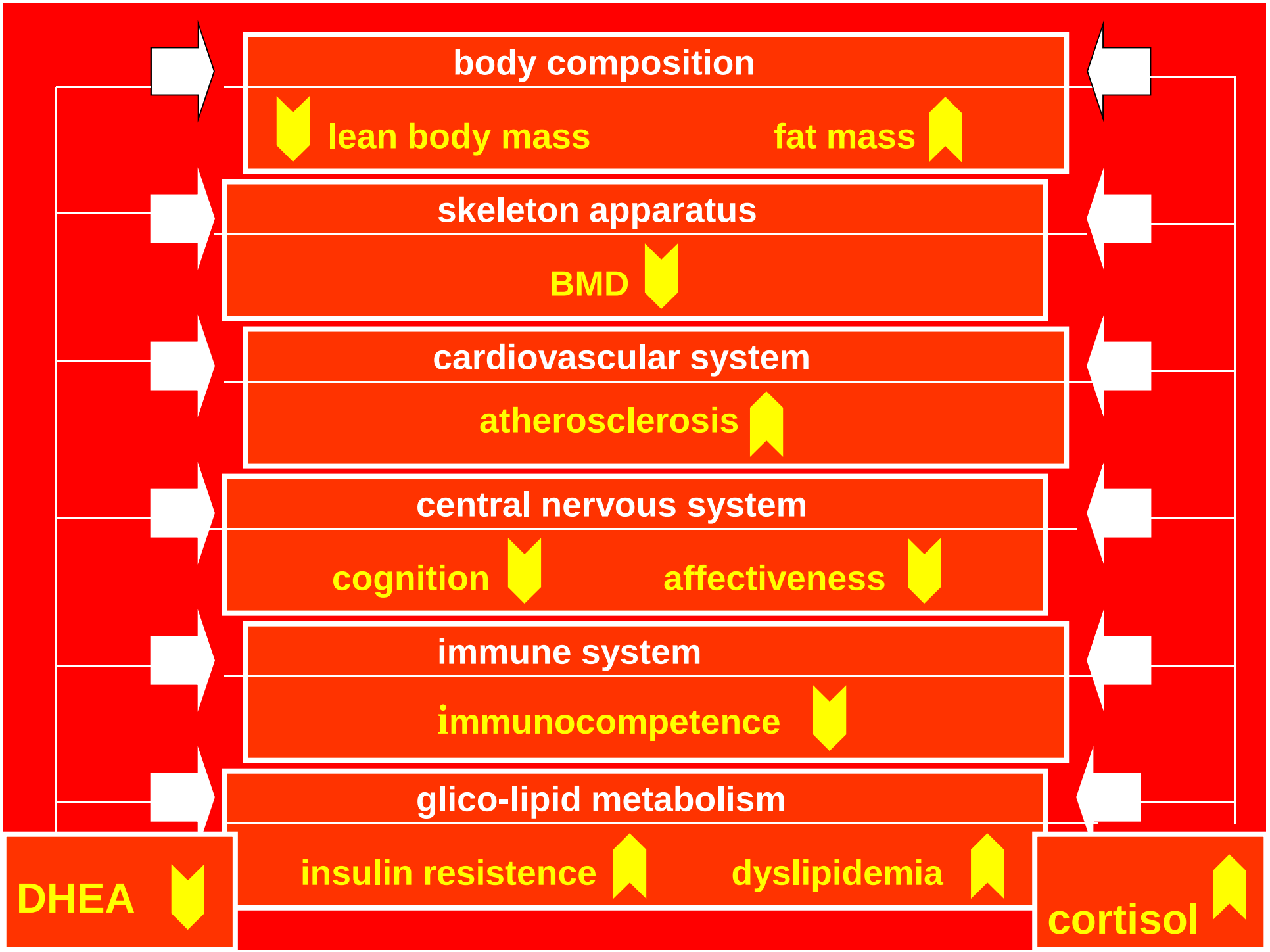
- DHEA → immuno activation (monocytes, B cell response, T cells expressing IL-2R) (Khorram 1997, Traish 2011)

- DHEA acute load effect on the immune response to influenza vaccination

→ positive response only in one of four studies (Degelau et al JAGS 1997; Evans et al Vaccine 1996; Danemberg JCEM 1997;Ben-Yehuda et al Mech Ag Dev 1998)

**Human RCTs** Only one study included parameters of immune function as Natural Killer cytotoxicity and lymphocyte cytokine production (Khanfer 2011)

→ only slight effects


body composition
lean body mass
fat mass
skeleton apparatus
BMD
cardiovascular system
atherosclerosis
central nervous system
cognition
affectiveness
immune system
immunocompetence
glico-lipid metabolism
insulin resistence
dyslipidemia
DHEA
cortisol

corticoadrenal age related changes

through two different parallel ways

DHEA ↓ ↑ Cortisol

can promote negative effects

⇒ on the same targets

⇒ with synergic action

globally defining the so called

**ADRENOPAUSE SYNDROME**

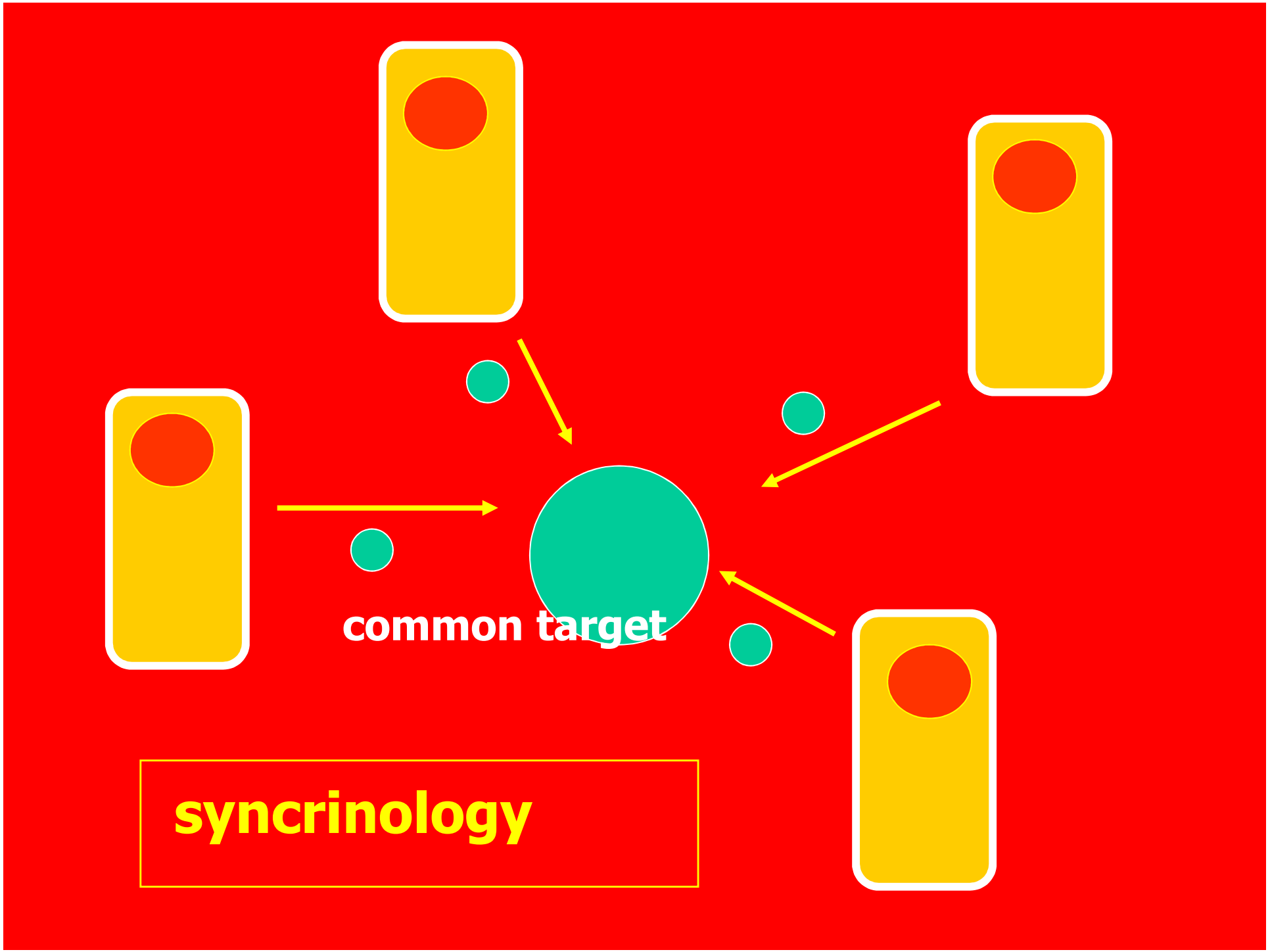
Endocrinology

Paracrinology

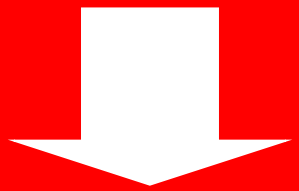
Autocrinology

Intracrinology

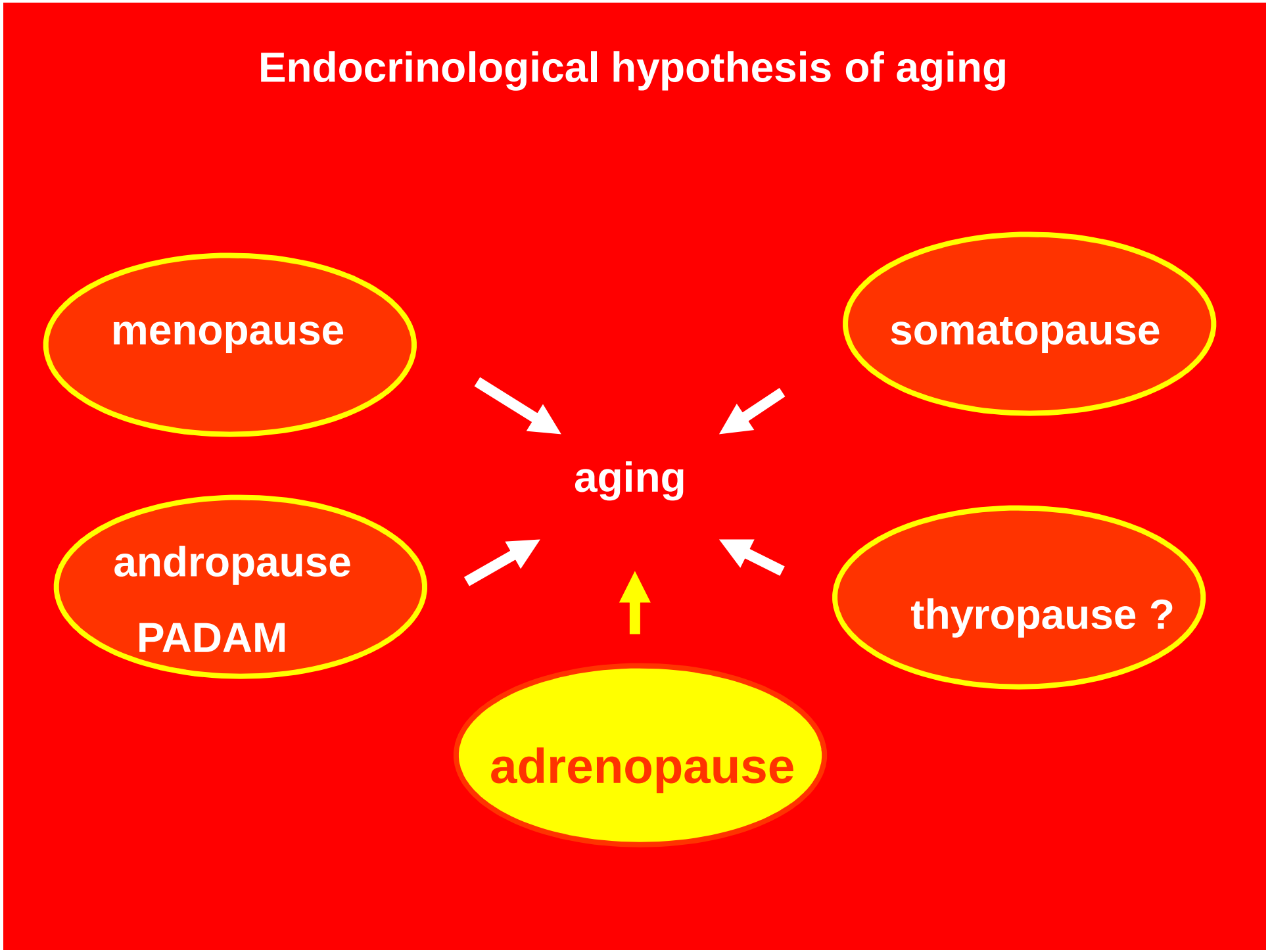
**Syncrinology**

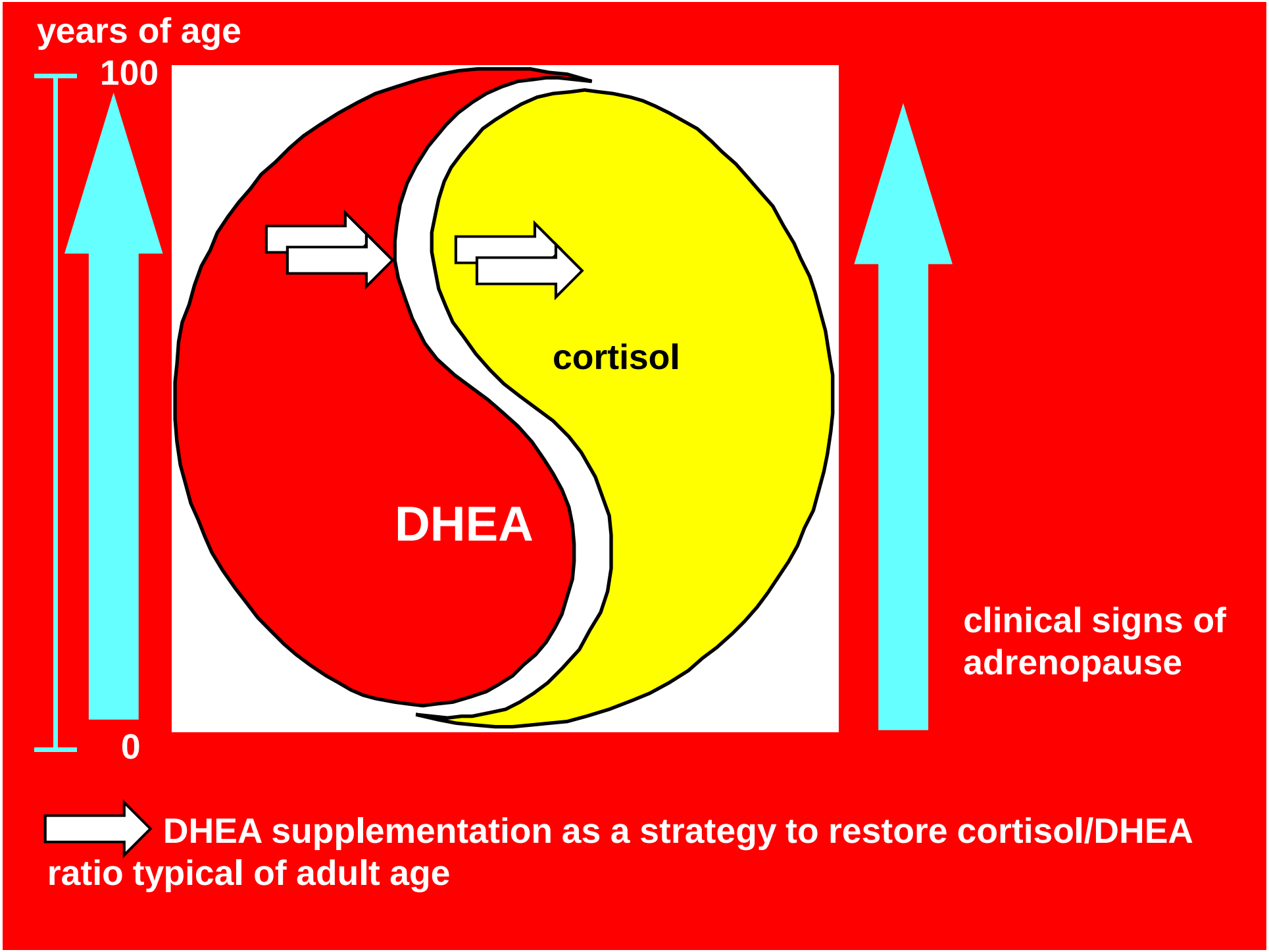

common target
syncrinology

**disruption of syncrinology**



**adrenopause**


Endocrinological hypothesis of aging
menopause
somatopause
aging
andropause
PADAM
thyropause ?
adrenopause


years of age
100
0
cortisol
DHEA
clinical signs of adrenopause
DHEA supplementation as a strategy to restore cortisol/DHEA ratio typical of adult age

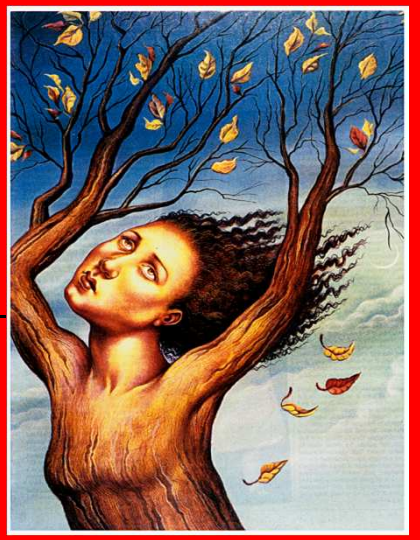
DHEA within daily routine

# Leitsymptome eines DHEA-Mangels

**Leistungsknick, Müdigkeit**
**Stressbelastbarkeit reduziert**

**Gedächtnisminderung**
**Depressivität**

**Libido reduziert**



**Trockene Haut**
**Nachlassende Behaarung**

**Atrophie Haut, Muskulatur, Organe**
**Cellulite, Hypermastie**

**Viszerale Fettzunahme**
**Muskel-Fett-Relation vermindert**

**Arthrose und Osteoporose**
**Anämie, Immundefizit**

= mentaler u. somatischer Vitalitätsmangel

verminderte Proteinsynthese - Zellproliferation - Zelldifferenzierung

Verdacht auf Androgenmangel bzw. Anabolika-Mangel im Alter

# Labordiagnostik

| | |
|---|---|
| Adrenopause | DHEA-S (DS)<br>DD: Cortisol |
| Gonadopause | Testosteron (freies; FAI), DHT<br>DD: LH, FSH |
| Somatopause | IGF-1 (für Wachstumshormon)<br>DD: Stress, Insomnie, orale Östrogene, Glykämie |

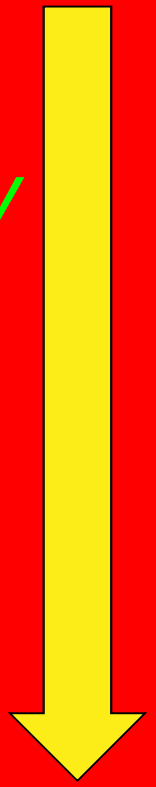
DHEA-S = Dehydro epi androsteron- Sulfat
DHT = Dihydrotestosteron
IGF-1 = Insulin-like Growth Factor-1

# Zeitlicher Verlauf von klinischen Effekten einer DHEA-Substitution

| Zielorgan | |
|---|---|
| ZNS | neuroaktives Steroid |
| Herz-Kreislauf | *kardio- u. gefäß-protektiv* |
| Haut | *Rejuvenation* |
| Immunität | *immunprotektiv* |
| Muskel / Fett | Body composition |
| Knochen | *osteoprotektiv* |

Zeitfaktor

6 Wo



>6 Mo

# Women : DHEA 25 mg/d and climateric Symptoms

| Kupperman-Index | | Vasomotor symptoms | Psychological symptoms | Total score |
|---|---|---|---|---|
| Group A early PMP | Before | 20.8 ± 2.2 | 9.3 ± 2.1 | 30.1 ± 3.5 |
| | 3 months | 13.6 ± 4.1[a] | 6.2 ± 1.0 | 19.6 ± 2.1[a] |
| | 6 months | 7.1 ± 2.5[a] | 3.7 ± 0.4[a] | 10.8 ± 1.6[a] |
| | 9 months | 6.7 ± 1.9[b] | 2.6 ± 0.2[b] | 9.3 ± 1.2[b] |
| | 12 months | 5.2 ± 1.0[b] | 1.8 ± 0.9[b] | 7.1 ± 0.9[b] |
| Group B late PMP | Before | 16.0 ± 2.4 | 8.6 ± 1.3 | 24.5 ± 3.8 |
| | 3 months | 12.5 ± 5.1 | 6.9 ± 0.8 | 19.4 ± 2.8[a] |
| | 6 months | 7.9 ± 2.5[b] | 5.5 ± 1.0[a] | 13.4 ± 1.8[a] |
| | 9 months | 5.5 ± 2.0[b] | 4.9 ± 0.4[a] | 10.8 ± 1.2[b] |
| | 12 months | 5.0 ± 1.1[b] | 3.1 ± 0.7[b] | 8.1 ± 0.9[b] |

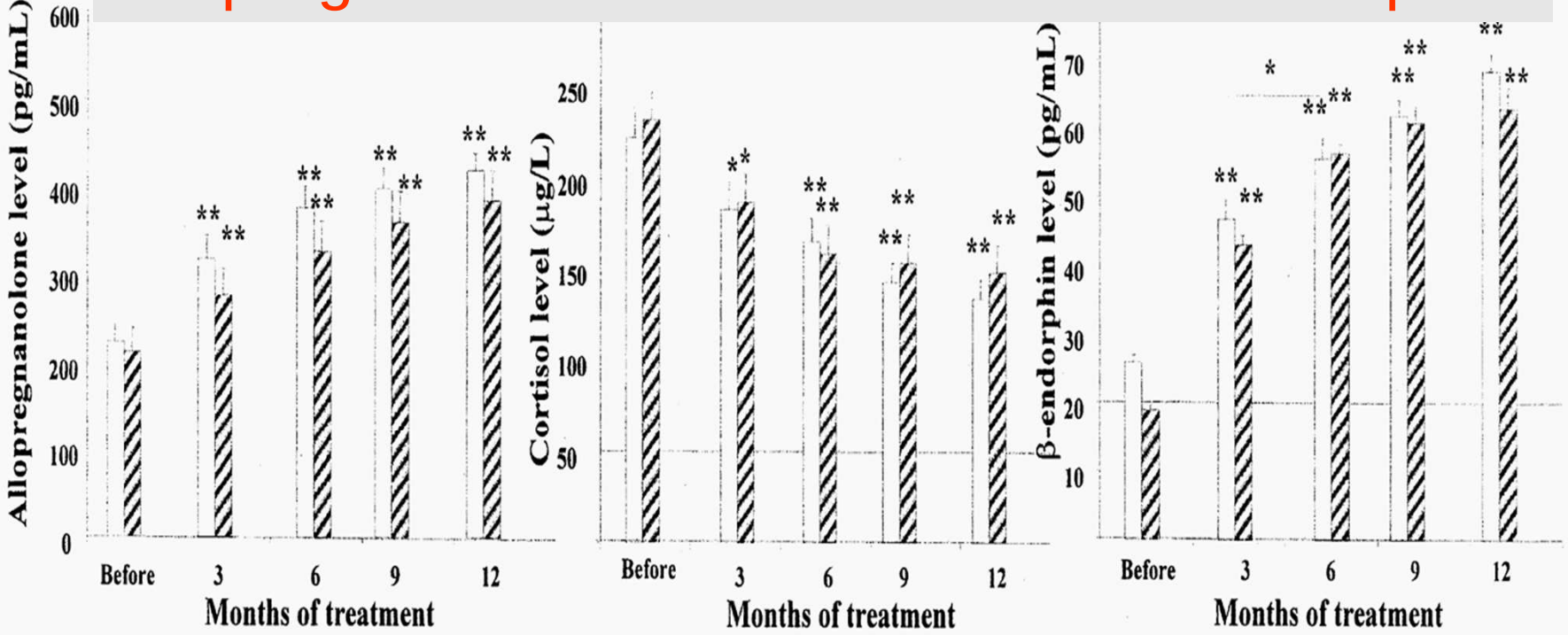
[a] $P<.05$ vs. before, [b] $P<.005$ vs. before.

Genazzani AD et al. 2003

# „well being“ changes after DHEA replacement

Mean ± SEM serum allopregnanolone (**A**), cortisol (F; **B**), and β-endorphin, before and after 3, 6, 9, and 12 months of oral DHEA supplementation (25 mg/d) in early postmenopausal women (group A) (□) and late postmenopausal women (group B) (▨). *$P<.05$; **$P<.005$.

Allopregnanolon Cortisol ß-Endorphin




*Genazzani. Low-dose DHEA supplementation and postmenopause. Fertil Steril 2003.*

# DHEA – Depression

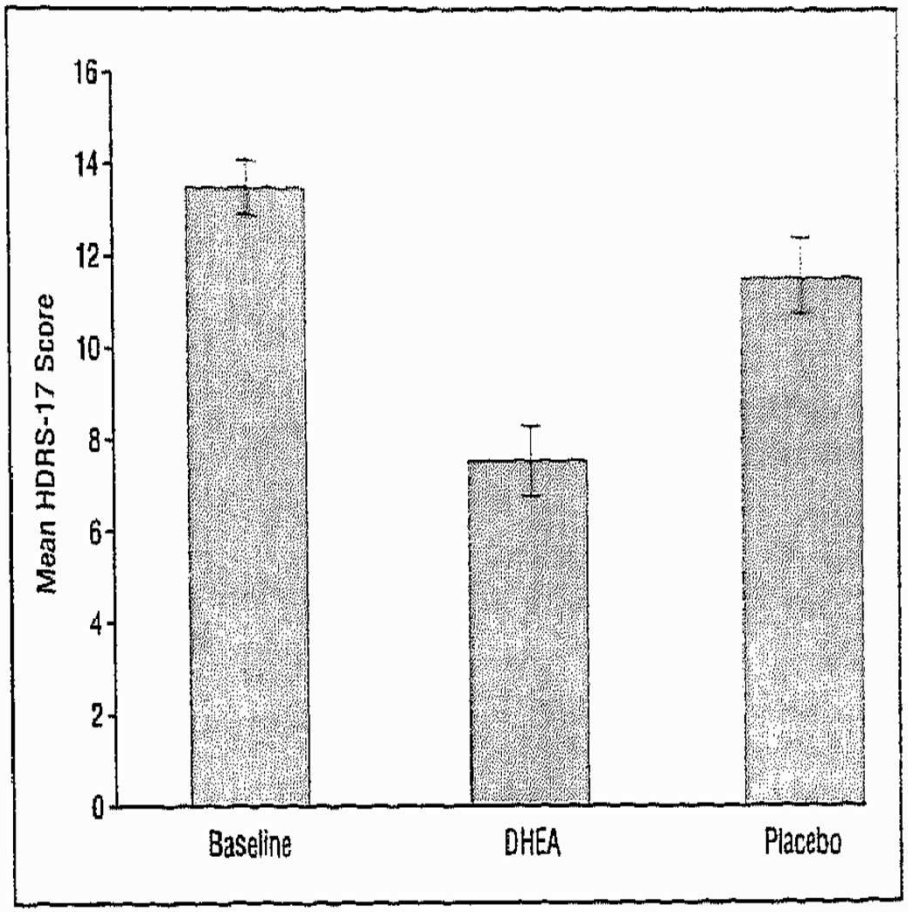



**Figure 2.** Six weeks of dehydroepiandrosterone (DHEA) treatment significantly improved 17-item Hamilton Depression Rating Scale (HDRS-17) scores compared with the baseline and placebo conditions ($F_{2,88}$=20.2 [$P$<.001]; DHEA vs baseline, $P$<.01; DHEA vs placebo, $P$<.01), whereas no significant effects were observed on HDRS-17 scale scores after 6 weeks of placebo compared with baseline conditions. Limit lines indicate standard error.

Schmidt PJ et al. 2005
National Institut of Mental Health, USA

23 men and
23 women (45-65J)

DHEA 6 weeks, crossover, Placebo, double blind, randomized,

Follow up 1 year

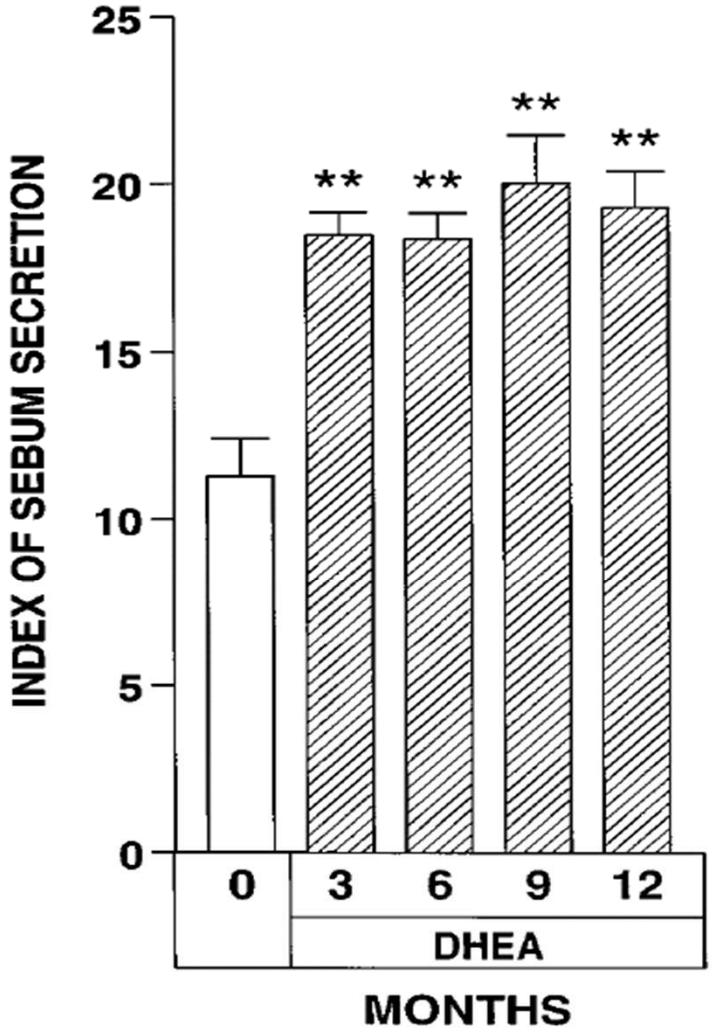
# DHEA-dematology (hair growth)

J Clin Endocrinol Metab. 2009 Apr;94(4):1182-90.

**Effects of dehydroepiandrosterone therapy on pubic hair growth and psychological well-being in adolescent girls and young women with central adrenal insufficiency: a double-blind, randomized, placebo-controlled phase III trial.**

CONCLUSIONS:
In adolescent girls with central adrenal insufficiency, daily replacement with 25 mg DHEA orally is beneficial:
Atrichia pubis vanishes, and psychological well-being improves significantly. Importantly, eight of the 10 Symptom Check-List-90-R scores, including those for depression, anxiety, and interpersonal sensitivity, and the global severity index improved in the DHEA group in comparison to the placebo group (P0.048). DHEA was well tolerated.

# DHEA-dematology (sebum secretion)




Labrie F
JCEM 1997

FIG. 8. Effect of percutaneous administration of DHEA for 6 and 12 months on the sebum secretion index measured with the Sebutape technique on six facial areas at the indicated time intervals.

# DHEA-dermatology (skin)

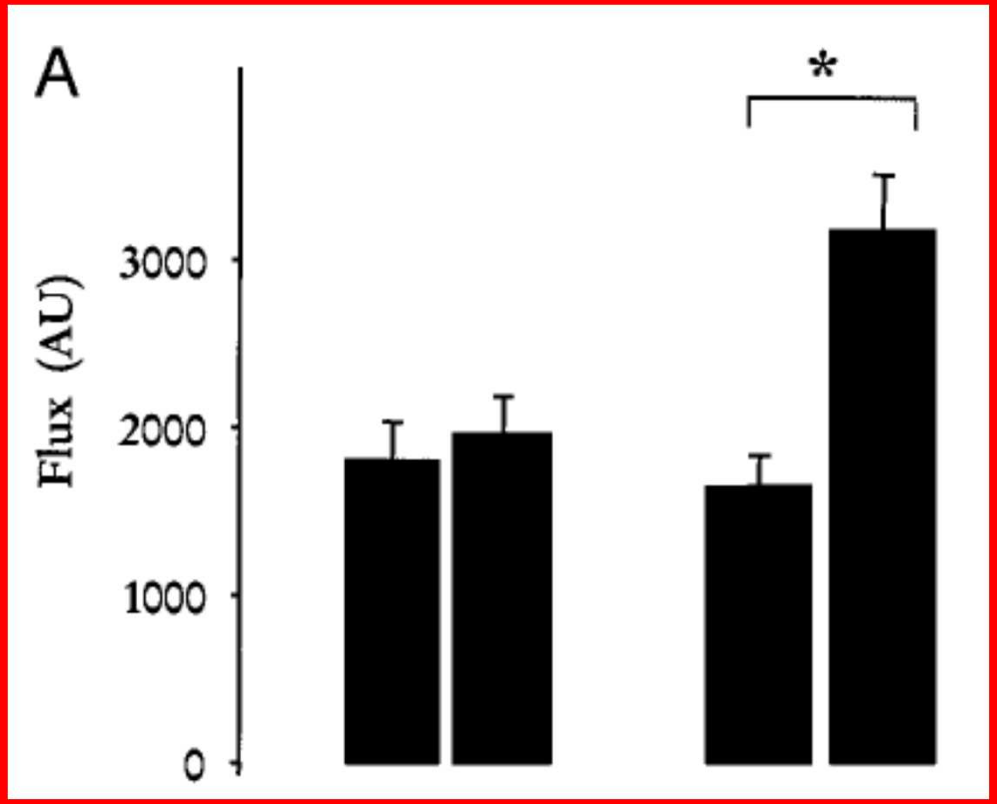
DHEAge Study: 280 wommen and men, 60-79 y,
50 mg DHEA oral/dd for 12 month
randomized, dounle blind, plazebo-controlled

Table 4. Skin study results at M12

| Measurement | Placebo | DHEA | *P* |
|---|---|---|---|
| All volunteers | | | |
| Sebum production, no. spots | 61 (11.7–132) | 101 (44.2–161.5) | 0.0008 |
| Skin hydration (forearm) | 71 (70.7–89.8) | 86 (74.5–96) | 0.01 |
| Skin pigmentation ($b^*$ face) | 15.9 (14.8–17.4) | 15.3 (14.2–16.6) | 0.02 |

Baulieu EE et al., Proc Natl Acad Sci (PNAS) 2000; 97:4279-84.

# DHEA and vessels




Williams et al.
JCEM 2004

postmenopausale women, n=36

100 mg DHEA/d oral
3 month, double blind, Placebo controlled, randomized

# DHEA and vessels

Kawano H et al. J Clin Endocrinol Metab 2003; 88: 3190-95.

25 mg DHEA-Supplementation improves endothelial function and insulin sensitivty in men

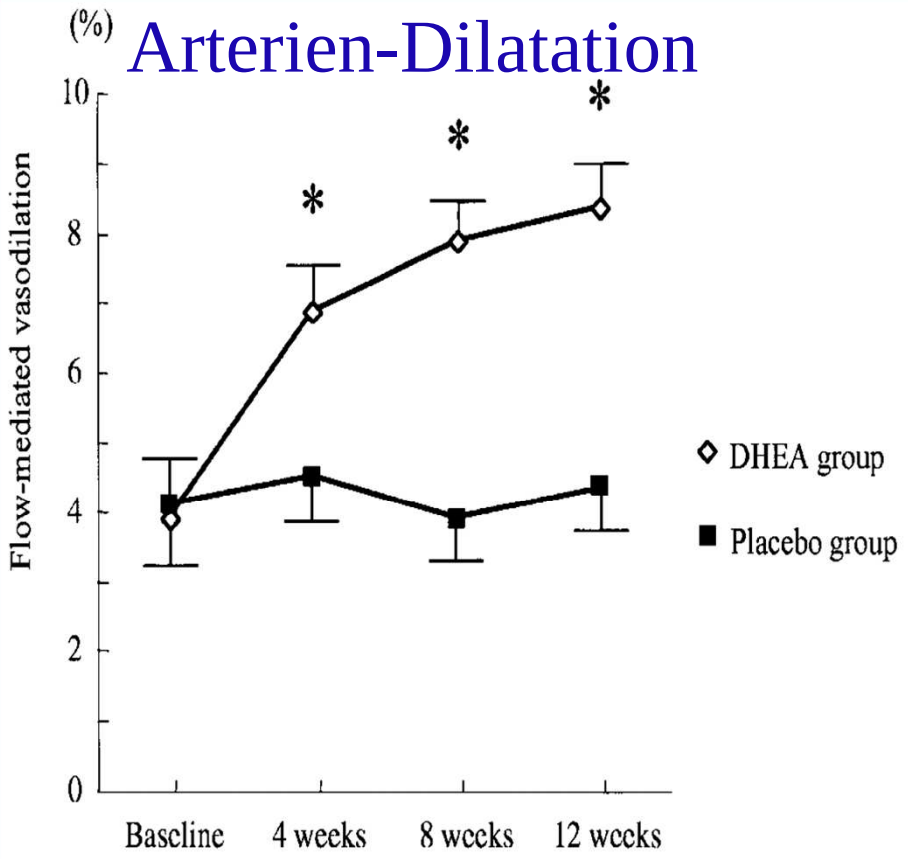



FIG. 1. Effects of DHEA supplementation on flow-mediated, endothelium-dependent dilation of the brachial artery. *, $P < 0.01$ *vs.* baseline. Data are expressed as the mean ± SE.

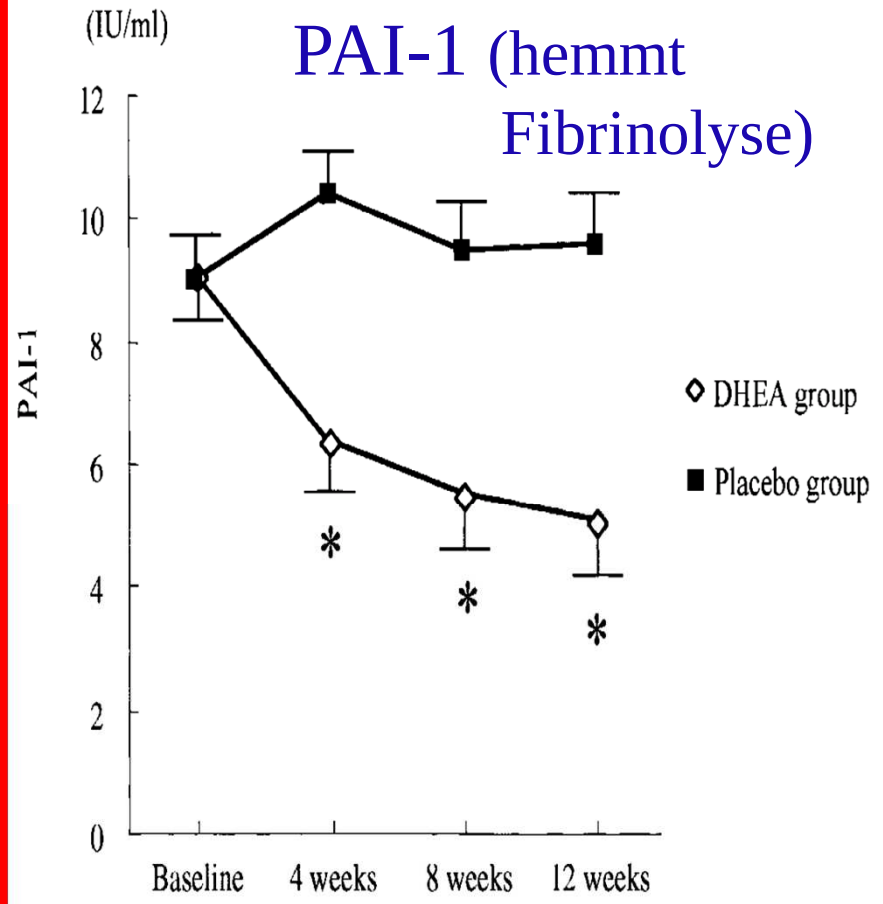



FIG. 2. Effects of DHEA supplementation on plasma PAI-1 concentration. *, $P < 0.01$ *vs.* baseline. Data are expressed as the mean ± SE.

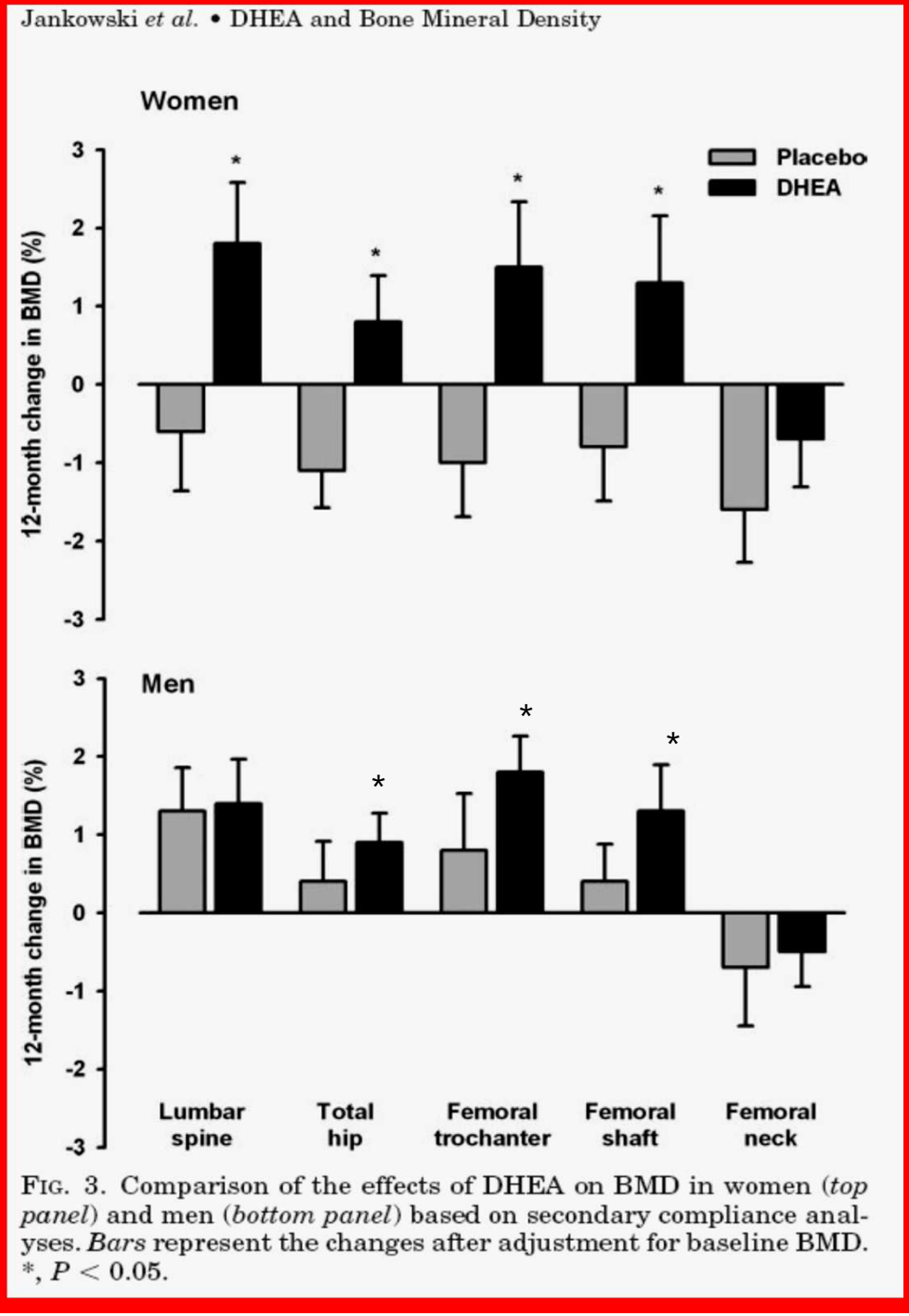



FIG. 3. Comparison of the effects of DHEA on BMD in women (*top panel*) and men (*bottom panel*) based on secondary compliance analyses. *Bars* represent the changes after adjustment for baseline BMD. *, $P < 0.05$.

Jankowski CM et al. JCEM 2006
Jankowski CM et al. JCEM 2008

# Bone density

70 men and 70 women
60-88 years
Low DHEA-S

50 mg DHEA or placebo
12 month, randomisiert

Lumbar-Zunahme bei Männern
nicht sign. wg Plazebo-Effekte

# DHEA-mechanism of action:

Jankowski et al. 2008

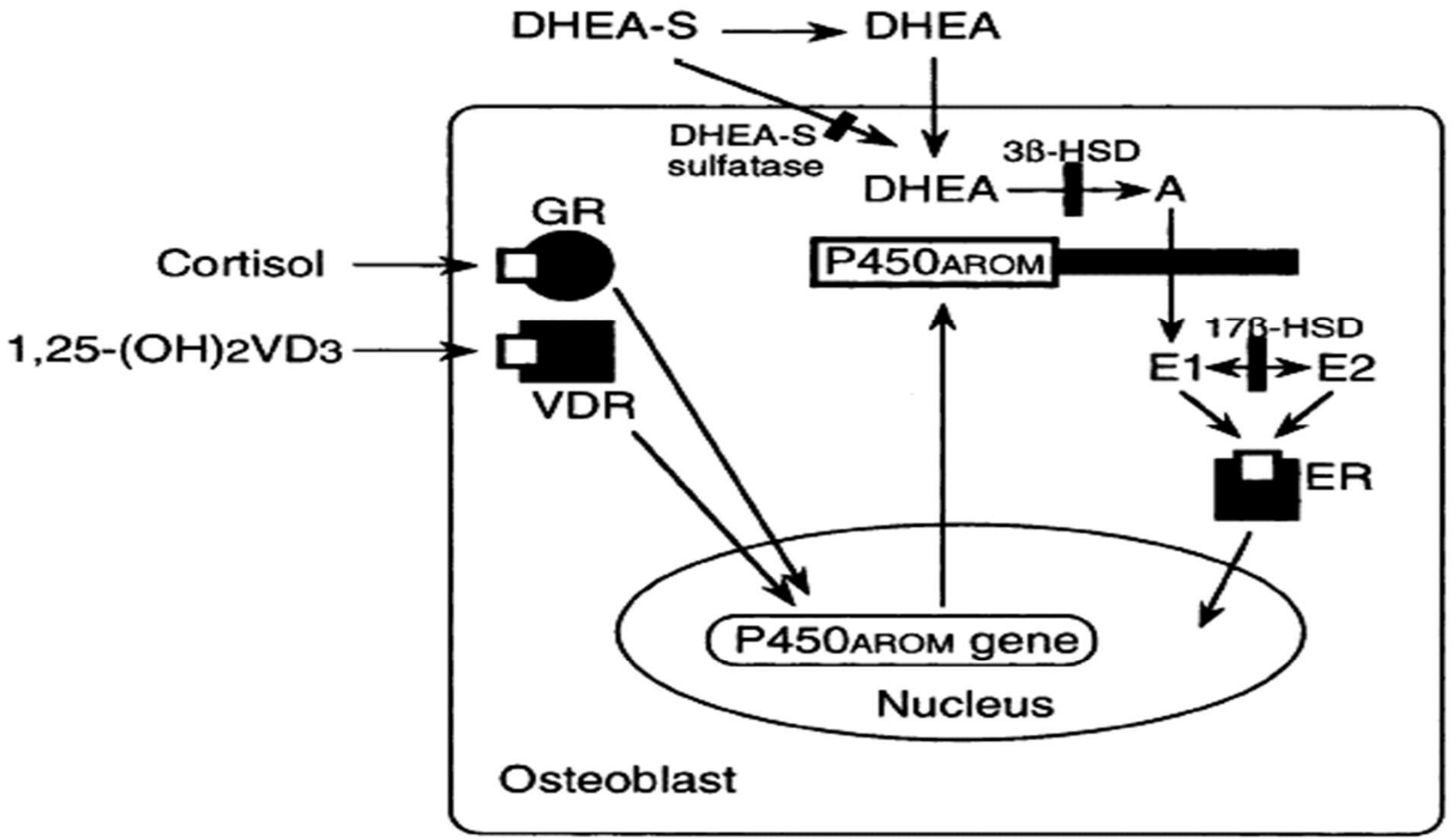



Fig. 5. Schematic representation of intracrine formation of estrogen from DHEA-S in osteoblast. GR, glucocorticoid

# DHEA-Darreichung

## intramuskulär

Einheitsdosis DHEA + Estrogen

seit 1974 in D. zugelassen,

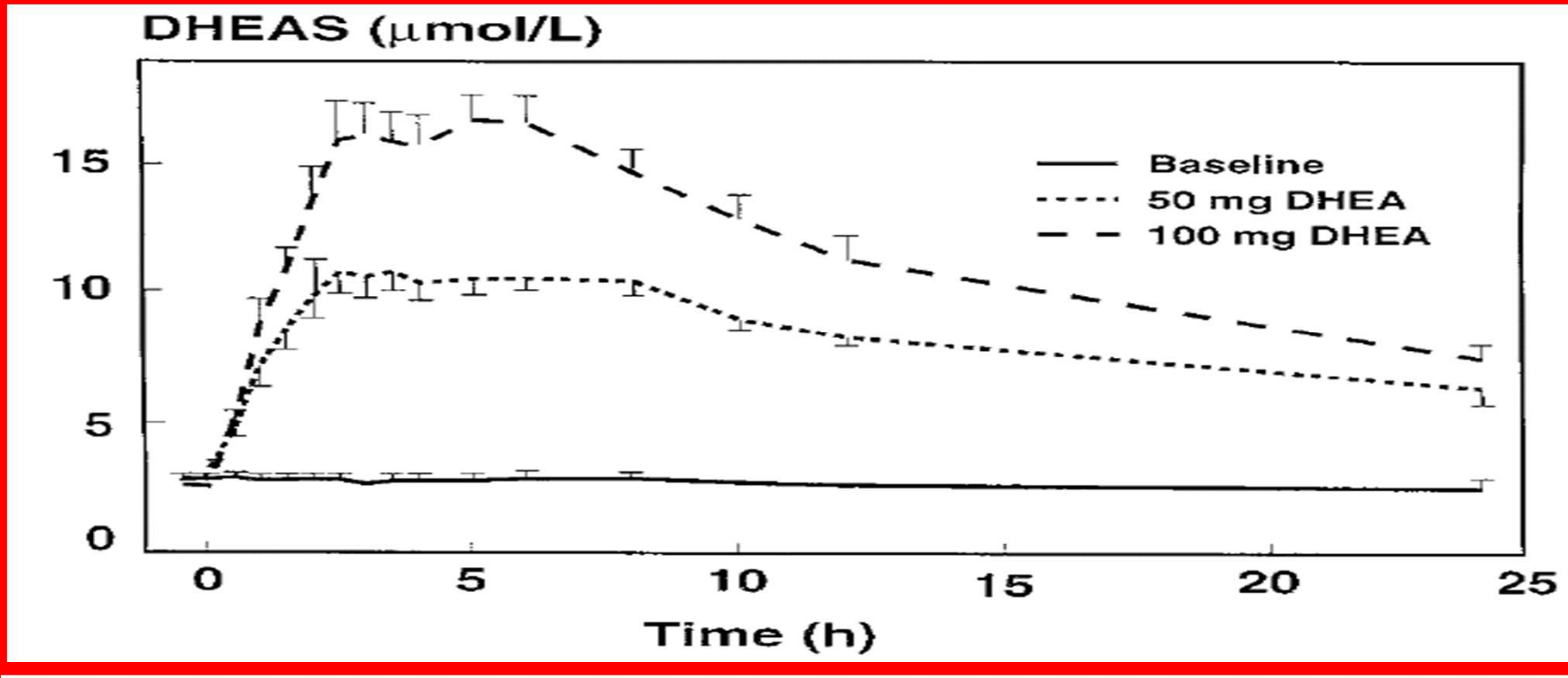
etabliert, von Kassen bezahlt

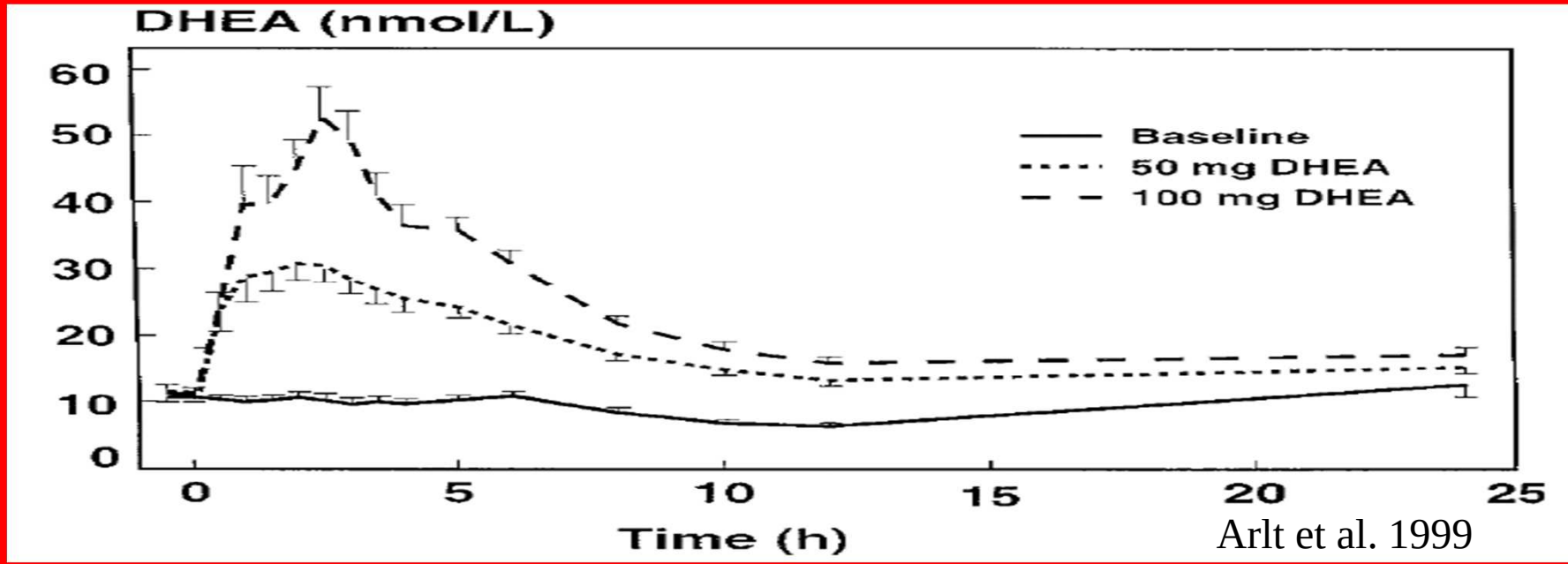

## oral (transdermal, sublingual)

- auf Rezeptur möglich (Apotheke)
- Bezug als ausländisches Präparat

Apotheke; Botendienst;
Nahrungsergänzung USA

→ höhere Aufklärungsanforderungen beachten




Arlt et al. 1999

# Individuell angepasste Dosierung ratsam
## - Blutkontrolle 3-5 Stunden nach DHEA -

**Tabelle 3.** Individuell adjustierte DHEA-Substitution (5–100 mg): Häufigkeitsverteilung einer oralen DHEA-Dosis bei Adrenopause

| | 5 mg | 10 mg | 15 mg | 25 mg | 50 mg | 75 mg | 100 mg |
|---|---|---|---|---|---|---|---|
| Frauen, % | 18 | 26 | 34 | 19 | 3 | | |
| Männer, % | | | 5 | 13 | 51 | 17 | 14 |

Jeweils 100 Patienten zwischen 46 und 74 Jahren mit individuell fortgeschrittener Adrenopause. Substitution mit DHEA zur Einstellung auf Blutspiegel von DS zwischen 2 und 2,8 µg/ml bei Frauen und 4 und 5 µg/ml bei Männern, jeweils 3–5 h nach DHEA-Einnahme. Dargestellt Häufigkeitsverteilung der Dosierungen in Prozent. Römmler A., Hormonzentrum München, 2002.

Römmler A. Gynakol Geburtshilfliche Rundsch 2003; 43: 79-90

# Pleiotrophy of DHEA

F. Saad,*, C.E. Hoesl, M. Oettel, J.-D. Fauteck, A. Römmler

European Urology 48; 724-33; 2005



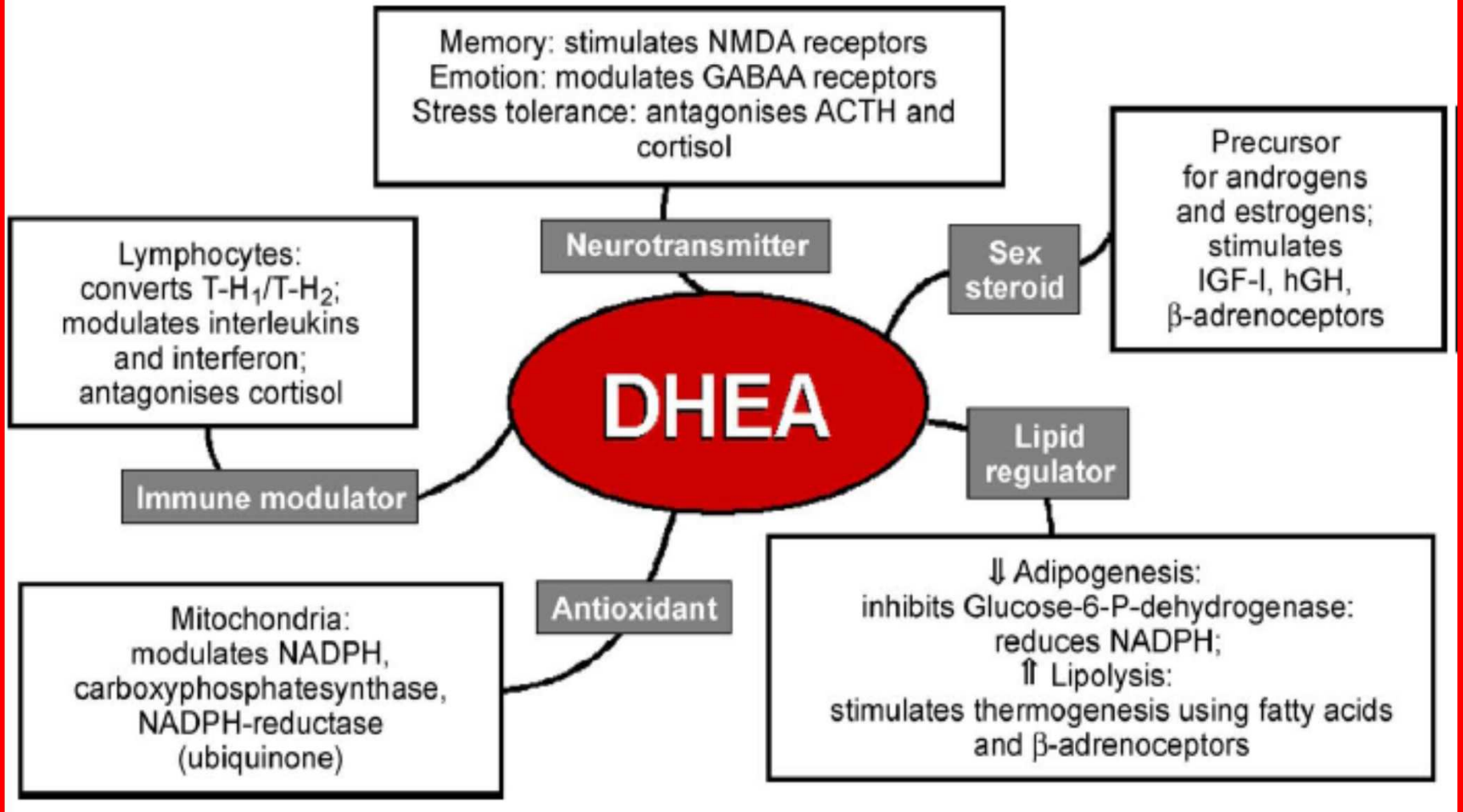



Fig. 2. Mechanisms of action of DHEA.

Herzlichen Dank
für Ihre Aufmerksamkeit!

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Anti-Aging Medicine

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