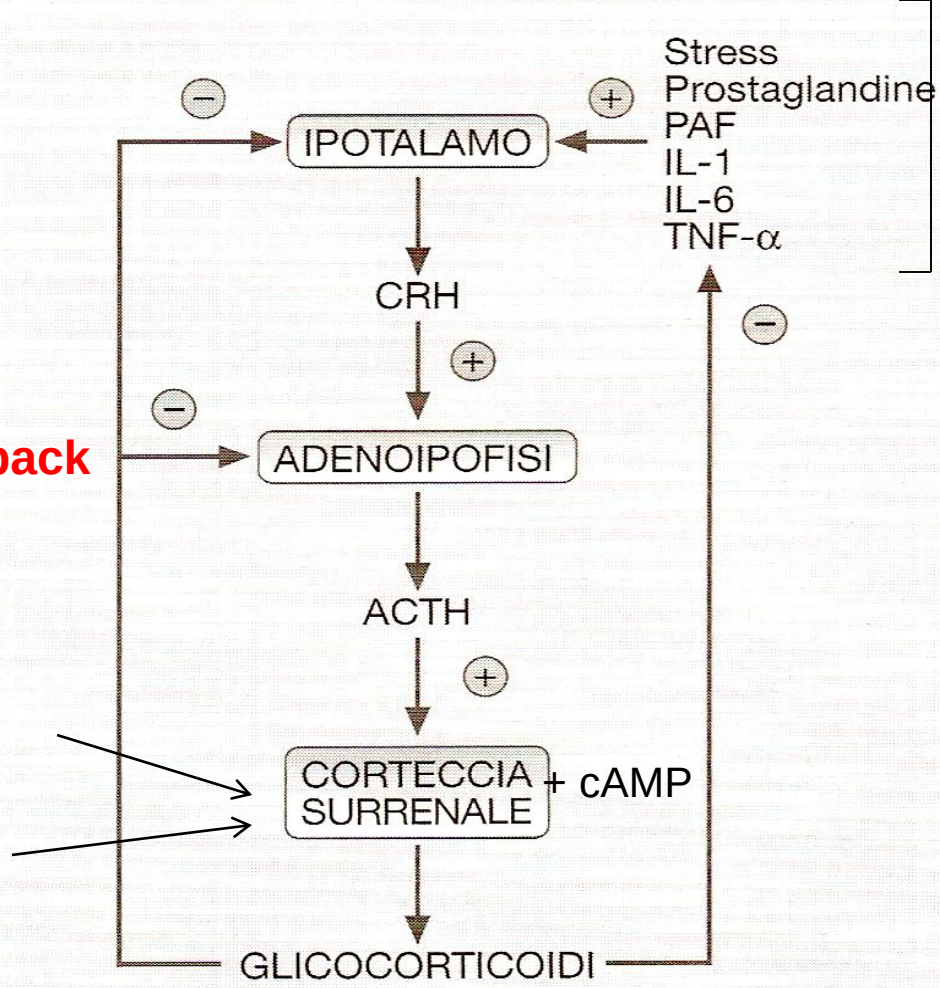
GLUCOCORTICOIDS

2
Negative feedback

Mineralo-corticoids (Glomerulosa)
Glucocorticoids (Fasciculata)



inflammatory responses 1
infections

Negative feedback 2

Fig. 1. Asse ipotalamo-ipofisi-surrene. Stimoli stressogeni, mediatori lipidici, citochine stimolano a livello ipotalamico la produzione di CRH, che stimola la adenoipofisi a produrre ACTH, che, a sua volta, induce un aumento della sintesi di ormoni corticosurrenalici. I glicocorticoidi inibiscono con vari meccanismi a livello sia ipotalamico che ipofisario la sintesi e l'attività biologica di CRH ed ACTH ed inoltre bloccano la sintesi di mediatori e citochine. Con tale meccanismo a *feedback* negativo i glicocorticoidi sono in grado di controllare l'attivazione dell'asse ipotalamo-ipofisi-surrene e quindi la propria sintesi.

Hypothalamic - pituitary gland - adrenal (HPA) Axis

Increase in Glucocorticoids

Glucocorticoids Synthesis Inhibitors

Metyrapone
Aminoglutethimide
Ketoconazole
Mitotane
Trilostane

Cushing Syndrome

Receptor Antagonists

Mifepristone
(RU 486)

Asthenia and easy fatigability due to increased protein, bone and skin catabolism; osteoporosis, weight gain with obesity, particularly at the trunk and face level; loss of libido, impotence, frigidity; hypertension; amenorrhea, dysmenorrhea and hirsutism in women; hyperglycemia, type II diabetes mellitus and glucose intolerance; psychological problems (depression, psychosis, nervousness and irritability); skin problems with areas of atrophy and reddish-purple streaks typical on the hips on the abdomen and lower limbs, seborrhea; bone and joint pains; lengthening of the healing time and tendency to infections (decrease in lymphocytes)

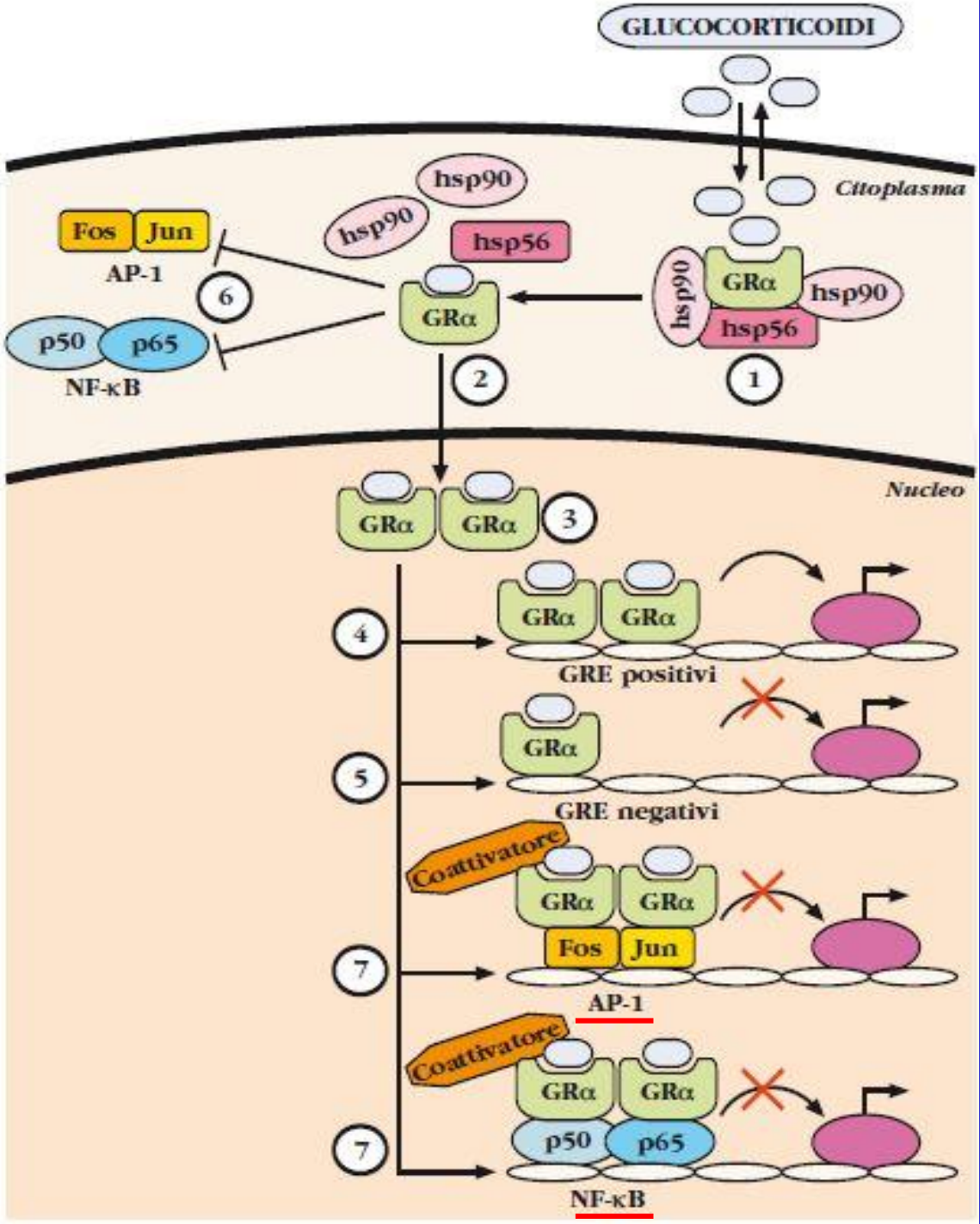
Metabolic actions

- *Carbohydrates*: decreased uptake and utilisation of glucose accompanied by increased gluconeogenesis; this causes a tendency to hyperglycaemia.
- *Proteins*: increased catabolism, reduced anabolism.
- *Lipids*: a permissive effect on lipolytic hormones and a redistribution of fat, as observed in Cushing's syndrome.

Regulatory actions

- *Hypothalamus and anterior pituitary gland*: a negative feedback action resulting in reduced release of endogenous glucocorticoids.
- *Cardiovascular system*: reduced vasodilatation, decreased fluid exudation.
- *Musculoskeletal*: decreasing osteoblast and increasing osteoclast activity.
- *Inflammation and immunity*:
  - *acute inflammation*: decreased influx and activity of leucocytes
  - *chronic inflammation*: decreased activity of mononuclear cells, decreased angiogenesis, less fibrosis
  - *lymphoid tissues*: decreased clonal expansion of T and B cells, and decreased action of cytokine-secreting T cells.
- *Mediators*:
  - decreased production and action of cytokines, including interleukins, tumour necrosis factor-α and granulocyte macrophage colony-stimulating factor
  - reduced generation of eicosanoids
  - decreased generation of IgG
  - decrease in complement components in the blood
  - increased release of anti-inflammatory factors such as interleukin-10 and annexin 1.
- *Overall effects*: reduction in the activity of the innate and acquired immune systems, but also decreased healing and diminution in the protective aspects of the inflammatory response.

Glucocorticoids



Mechanism of action of glucocorticoids

Coactivators:
SRC (steroid),
GRIP (glucocorticoid)
CBP (cAMP)

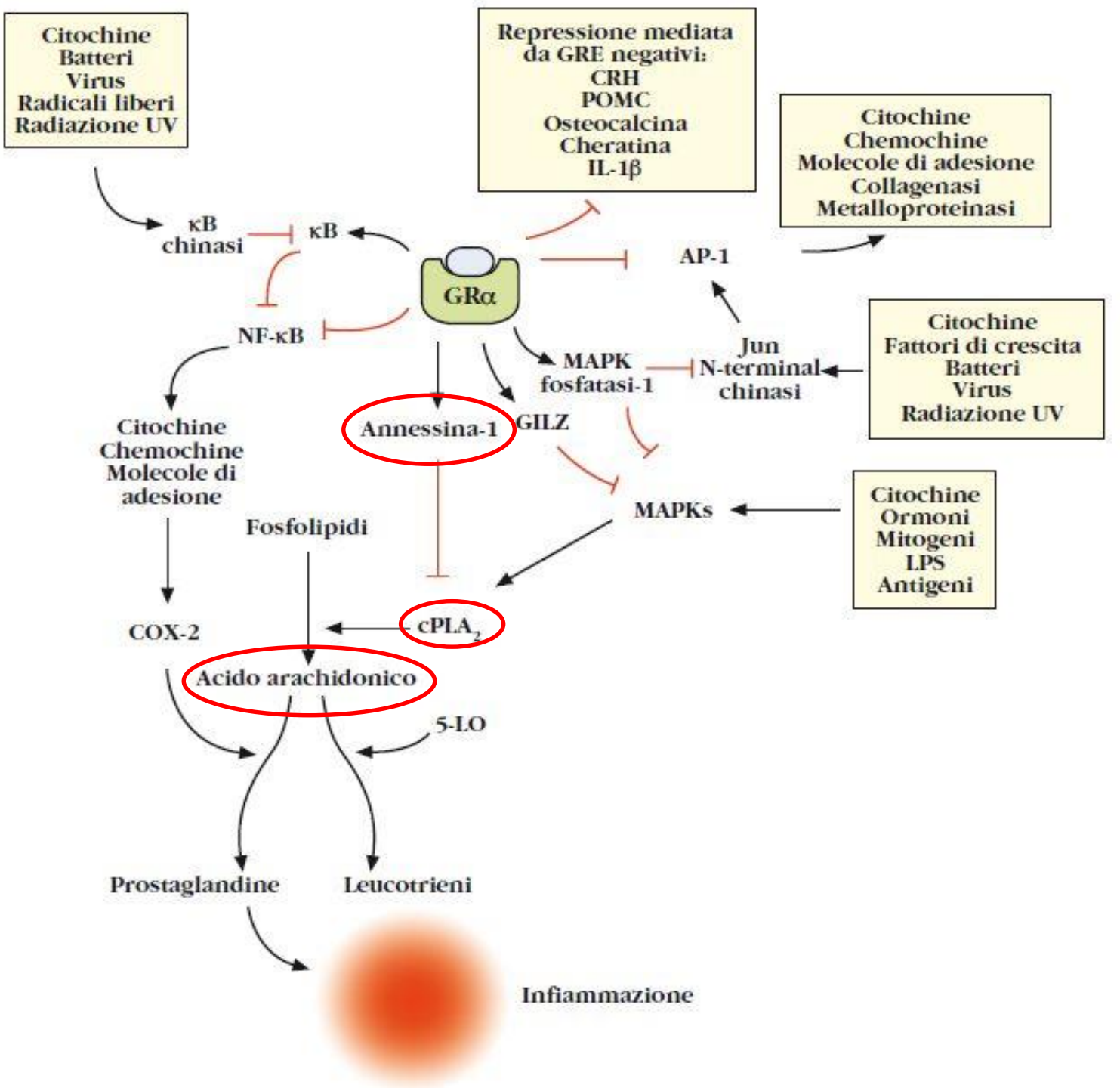
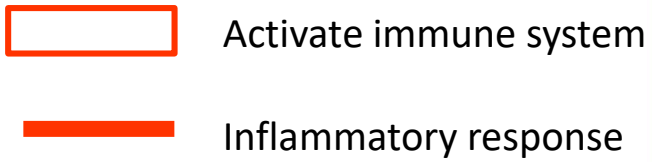

Citochine
Batteri
Virus
Radicali liberi
Radiazione UV
Repressione mediata da GRE negativi:
CRH
POMC
Osteocalcina
Cheratina
IL-1β
Citochine
Chemochine
Molecole di adesione
Collagenasi
Metalloproteinasi
κB chinasi
κB
AP-1
GRα
NF-κB
MAPK fosfatasi-1
Jun N-terminal chinasi
Citochine
Fattori di crescita
Batteri
Virus
Radiazione UV
Citochine
Chemochine
Molecole di adesione
Annessina-1
GILZ
MAPKs
Citochine
Ormoni
Mitogeni
LPS
Antigeni
Fosfolipidi
COX-2
cPLA2
Acido arachidonico
5-LO
Prostaglandine
Leucotrieni
Infiammazione
Inhibition
Stimulation

Tabella 47.3. Meccanismo antinfiammatorio ed immunosoppressore dei glucocorticoidi.

INIBIZIONE DELLA SINTESI DI PROTEINE PROINFIAMMATORIE ED IMMUNOSTIMOLANTI	INDUZIONE DELLA SINTESI DI PROTEINE ANTINFIAMMATORIE ED IMMUNODEPRESSIVE
Citochine e recettori IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-12 TNFα, IFNγ Recettori per IL-2	Annessina-1 * Recettore di tipo II per IL-1 IκBα GILZ MAPK fosfatasi-1
Chemochine IL-8 MCP-1	
Fattori di crescita GM-CSF G-CSF	
Molecole di adesione E-selectin ELAM-1 ICAM-1	
Enzimi Fosfolipasi A_2 Cicloossigenasi inducibile Nitrossidosintasi inducibile Collagenasi Metalloproteinasi	



IL=interleuchina, TNF-α=tumor necrosis factor-α, IFN-γ=interferone-γ, MCP-1=monocyte chemotactic protein-1, GM-CSF=granulocyte-macrophage colony stimulating factor, G-CSF=granulocyte colony stimulating factor, ELAM-1=endothelial-leukocyte adhesion molecule-1, ICAM-1=intercellular adhesion molecule-1.

- Glucocorticoids bind intracellular receptors that then dimerise, migrate to the nucleus, and interact with DNA to modify gene transcription, inducing synthesis of some proteins and inhibiting synthesis of others.
- *Metabolic actions*: most mediator proteins are enzymes, for example cAMP-dependent kinase, but not all actions on genes are known.
- *Anti-inflammatory and immunosuppressive actions*: known actions include:
  - inhibition of transcription of the genes for cyclo-oxygenase-2, cytokines and interleukins, cell adhesion molecules, and the inducible form of nitric oxide synthase
  - block of vitamin D_3-mediated induction of the osteocalcin gene in osteoblasts, and modification of transcription of the collagenase genes
  - increased synthesis and release of annexin-1, which has potent anti-inflammatory effects on cells and mediator release, and may also mediate negative feedback at the level of the hypothalamus and anterior pituitary gland.
- Some rapid non-genomic effects of glucocorticoids have also been observed.

Mechanism of action

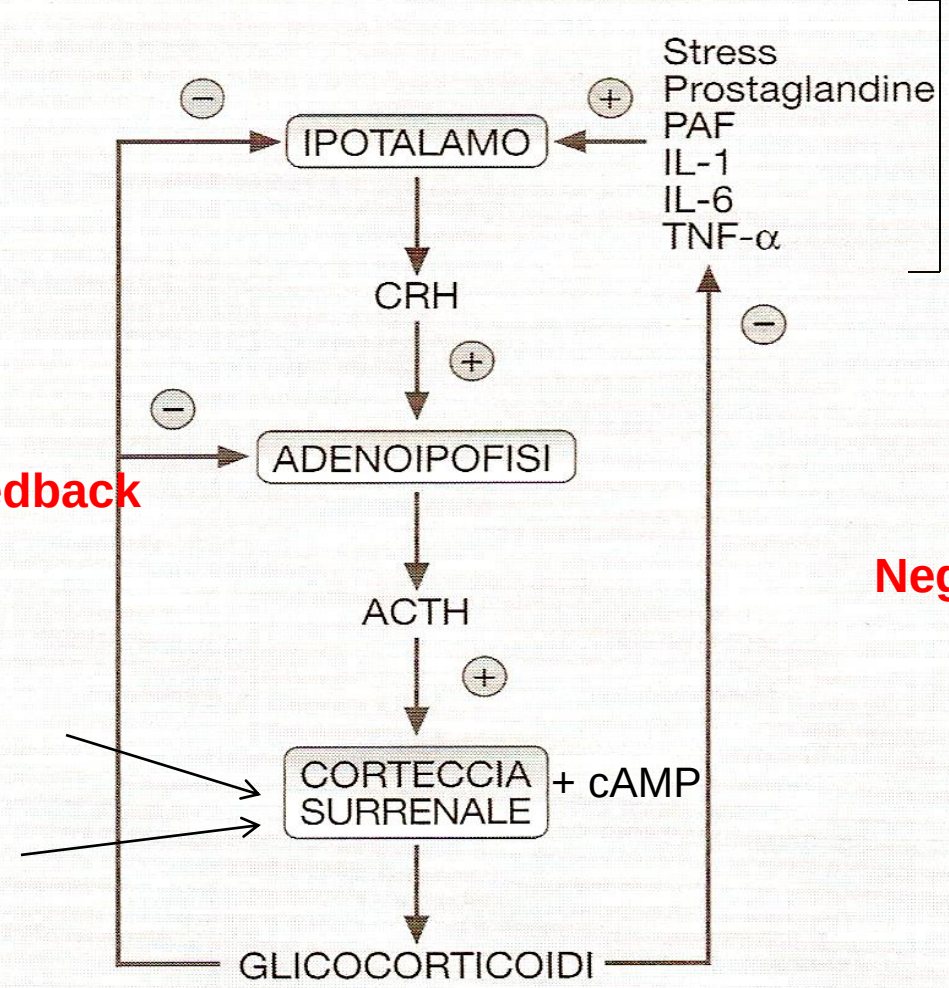


Fig. 1. Asse ipotalamo-ipofisi-surrene. Stimoli stressogeni, mediatori lipidici, citochine stimolano a livello ipotalamico la produzione di CRH, che stimola la adenoipofisi a produrre ACTH, che, a sua volta, induce un aumento della sintesi di ormoni corticosurrenalici. I glicocorticoidi inibiscono con vari meccanismi a livello sia ipotalamico che ipofisario la sintesi e l'attività biologica di CRH ed ACTH ed inoltre bloccano la sintesi di mediatori e citochine. Con tale meccanismo a *feedback* negativo i glicocorticoidi sono in grado di controllare l'attivazione dell'asse ipotalamo-ipofisi-surrene e quindi la propria sintesi.

inflammatory responses
infections

Negative Feedback

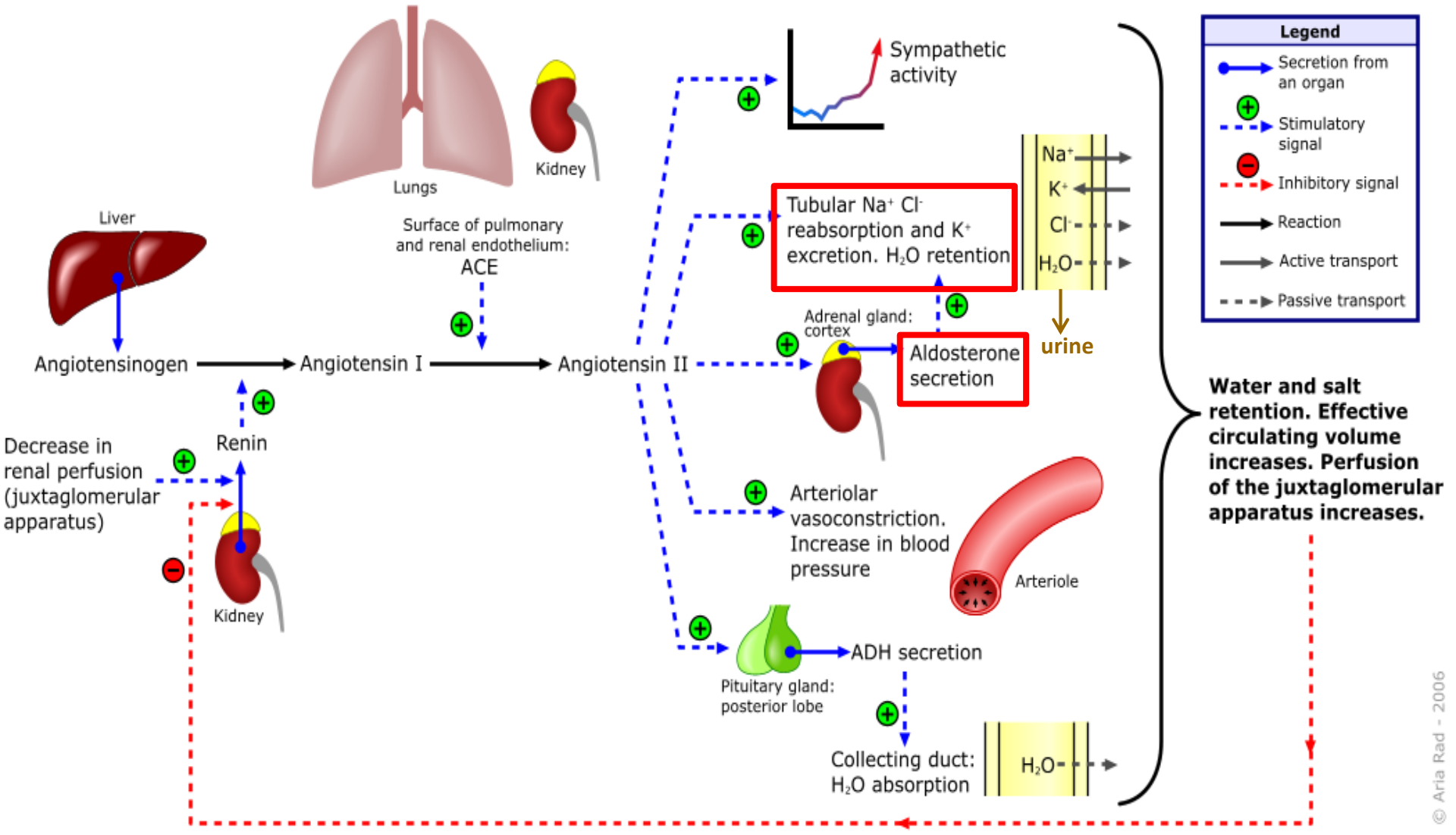
Negative Feedback

Mineralo-corticoids (Glomerulosa)

Hypothalamic - pituitary gland - adrenal (HPA) Axis

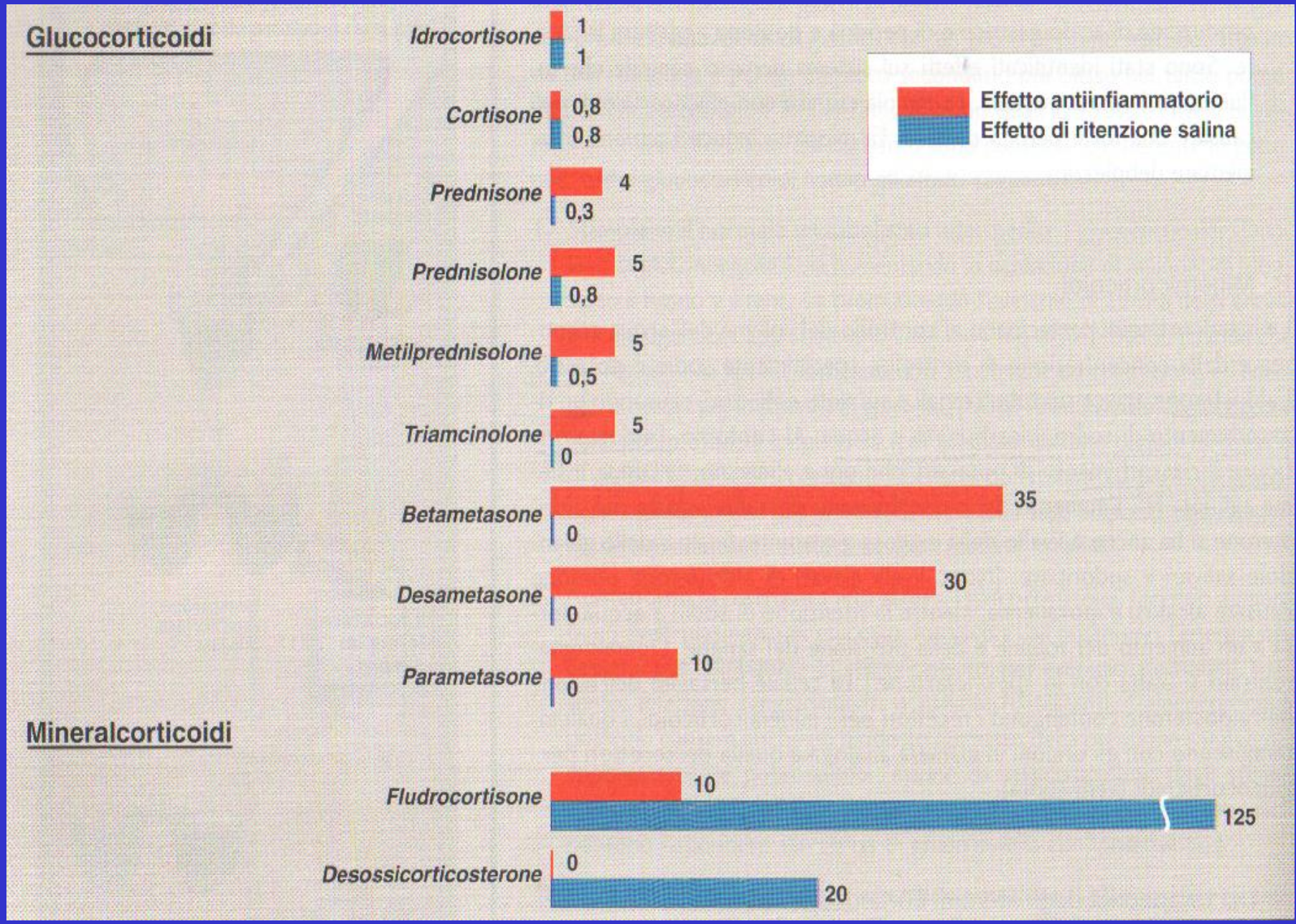
Mineralocorticoid Activity

Renin-angiotensin-aldosterone system



CORTICOSTEROID DRUGS

Compound	Relative affinity for glucocorticoid receptors[a]	Approximate relative potency in clinical use		Duration of action after oral dose[b]	Comments
		Anti-inflammatory	*Sodium retaining*		
Hydrocortisone (cortisol)	1	1	1	Short	Drug of choice for replacement therapy
Cortisone	0.01	0.8	0.8	Short	Cheap; inactive until converted to hydrocortisone; not used as anti-inflammatory because of mineralocorticoid effects
Corticosterone	0.85	0.3	15	Short	–
Prednisolone *	2.2	4	0.8	Intermediate	Drug of choice for systemic anti-inflammatory and immunosuppressive effects
Prednisone	0.05	4	0.8	Intermediate	Inactive until converted to prednisolone
Methylprednisolone *	11.9	5	Minimal	Intermediate	Anti-inflammatory and immunosuppressive
Triamcinolone	1.9	5	None	Intermediate	Relatively more toxic than others
Dexamethasone *	7.1	30	Minimal	Long	Anti-inflammatory and immunosuppressive, used especially where water retention is undesirable (e.g. cerebral oedema); drug of choice for suppression of adrenocorticotrophic hormone production
Betamethasone *	5.4	30	Negligible	Long	Anti-inflammatory and immunosuppressive, used especially when water retention is undesirable
Deoxycortone	0.19	Negligible	50	–	–
Fludrocortisone	3.5	15	150	Short	Drug of choice for mineralocorticoid effects
Aldosterone	0.38	None	500	–	Endogenous mineralocorticoid


Glucocorticoidi
Idrocortisone
1
1
Cortisone
0,8
0,8
Prednisone
4
0,3
Prednisolone
5
0,8
Metilprednisolone
5
0,5
Triamcinolone
5
0
Betametasone
35
0
Desametasone
30
0
Parametasone
10
0
Effetto antiinfiammatorio
Effetto di ritenzione salina
Mineralcorticoidi
Fludrocortisone
10
125
Desossicorticosterone
0
20

- Replacement therapy for patients with adrenal failure (*Addison's disease*).
- Anti-inflammatory/immunosuppressive therapy
  - in *asthma*
  - topically in various inflammatory conditions of skin, eye, ear or nose (e.g. *eczema, allergic conjunctivitis* or *rhinitis*)
  - *hypersensitivity states* (e.g. severe allergic reactions)
  - in miscellaneous diseases with autoimmune and inflammatory components (e.g. *rheumatoid arthritis* and other 'connective tissue' diseases, *inflammatory bowel diseases*, some forms of *haemolytic anaemia, idiopathic thrombocytopenic purpura*)
  - to prevent *graft-versus-host disease* following organ or bone marrow transplantation.
- In *neoplastic* disease
  - in combination with cytotoxic drugs in treatment of specific malignancies (e.g. *Hodgkin's disease, acute lymphocytic leukaemia*)
  - to reduce cerebral oedema in patients with metastatic or primary *brain tumours* (**dexamethasone**)

Endocrinological indications

- Adrenocortical insufficiency (Addison's disease)
- Secondary adrenocortical insufficiency (panhypopituitarism)
- Androgenital syndrome

Rheumatological indications
(prednisolone, methotrexate)

- Systemic lupus erythematosus (SLE) *
- Polymyositis and Dermatomyositis *
- Vasculitis *
- Polymyalgia and rheumatic fever *
- Rheumatoid arthritis
- Sjogren's syndrome

* first choice drugs

Pneumological indications
(methylprednisolone, prednisolone)

- State of asthmatic disease
- Sarcoidosis (in active phase)
- Bronchial asthma (by inhalation)
- Interstitial pulmonary fibrosis (in active phase)

Nephrological indications
(prednisolone)

- Minimal change glomerulonephritis with nephrotic syndrome
- Secondary glomerulonephritis (SLE, cryoglobulinemia)
- Rapidly progressing glomerulonephritis
- Membranous glomerulonephritis with nephrotic syndrome
- Local sclerosing glomerulonephritis with nephrotic syndrome

Dermatological indications

- Pemphigus *
- Bullous pemphigoid *
- Erythroderma *
- Eczema
- Acute urticaria
- Angioedema
- Erythema multiforme
- Atopic dermatitis
- Chronic lichen simplex
- Toxic epidermal necrolysis

* administered systemically only in severe episodes

Gastrointestinal and hepatic indications
(hydrocortisone, prednisone)

- Ulcerative colitis (in active phase)
- Crohn's disease (in active phase)
- Chronic active hepatitis
- Cholestatic viral hepatitis

Haematological indications

- Acute leukemias
- Hodgkin's and non-Hodgkin's lymphomas
- Autoimmune hemolytic anemias
- Idiopathic purpura
- Thrombocytopenia
- Multiple myeloma
- Aplastic anemia
- Agranulocytosis

Infectious indications *

- Septicemia from gram-negative bacteria with excessive inflammatory response
- Haemophilus influenzae meningitis
- Viral meningoencephalitis
- Pneumocystis carinii pneumonia
- Infectious mononucleosis
- Tuberculosis with exudative component

*In bacterial infections, treatment should be combined with antibiotics

Pharmacokinetics and unwanted actions of the glucocorticoids

- Administration can be oral, topical or parenteral. The drugs are transported in the blood by corticosteroid-binding globulin and enter cells by diffusion. They are metabolised in the liver.
- Unwanted effects are seen mainly after prolonged systemic use as anti-inflammatory or immunosuppressive agents but not usually with replacement therapy. The most important are:
  - suppression of response to infection
  - suppression of endogenous glucocorticoid synthesis
  - metabolic actions
  - osteoporosis
  - iatrogenic Cushing's syndrome

Corticosteroids: therapeutic utilization

Risk-benefit

Dosage-Duration of therapy suspension

Metabolism alteration:

-increased gluconeogenesis + glucose in the blood (diabetes)

-lipolysis (free fat increase)

-organic defenses; Immune system

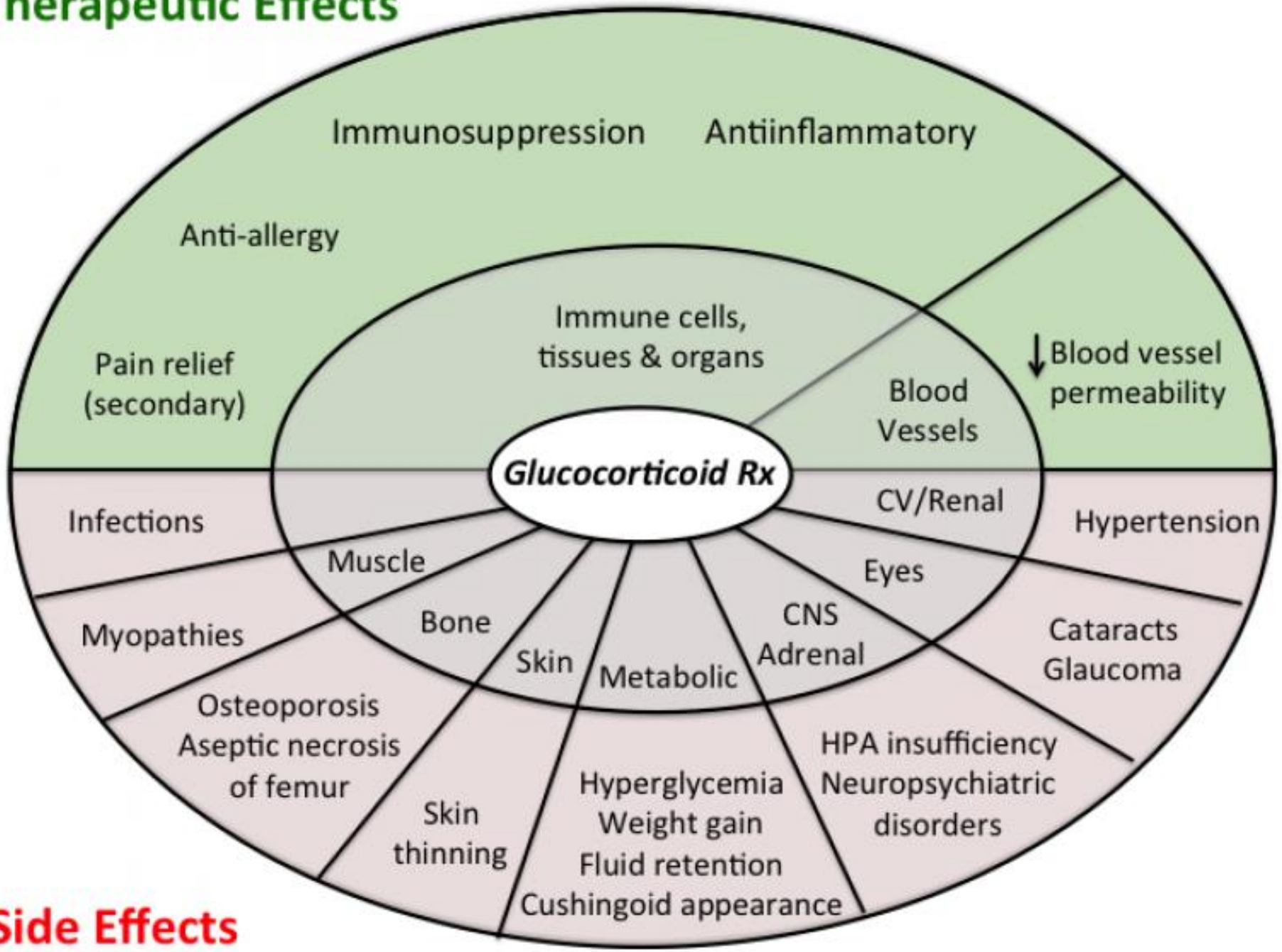
-tissue repair processes

- lymphocytes, eosinophils, monocytes, basophils (polymorphonuclear leukocytes ↑)

-renal function HPA (suspension)

-suspension syndrome: (arthralgia, myalgia, fever)

Side Effects


Therapeutic Effects
Immunosuppression
Antiinflammatory
Anti-allergy
Pain relief
(secondary)
Immune cells,
tissues & organs
Blood vessel
permeability
Blood
Vessels
Glucocorticoid Rx
Infections
CV/Renal
Hypertension
Muscle
Eyes
Myopathies
Bone
CNS
Adrenal
Cataracts
Glaucoma
Skin
Metabolic
Osteoporosis
Aseptic necrosis
of femur
HPA insufficiency
Neuropsychiatric
disorders
Skin
thinning
Hyperglycemia
Weight gain
Fluid retention
Cushingoid appearance
Side Effects

Decalogue for the administration of glucocorticoids

1) To be utilized only after a definite diagnosis
2) The therapeutic dose has to be defined step by step
3) Administration of drugs should be at the lowest effective dose for the shortest time. Best time of the day 8:00 am
4) Administration should be every other day as soon as possible
5) Reduce intake of food to prevent gain in weight
6) Reduce Na intake to prevent edema. If necessary increase intake of K
7) When possible, integrate NSAID and reduce glucocorticoid dose
8) Severity of side effects increases with dose and time of administration
9) Avoid sudden interruptions
10) Administration of high dose for only 1 week causes negligible side effects

IMMUNOSUPPRESSANTS

Clinical use of immunosuppressants

- Immunosuppressants are used for three main purposes:
  - —to suppress rejection of transplanted organs and tissues (kidneys, bone marrow, heart, liver, etc.)
  - —to suppress graft-versus-host disease (i.e. the response of lymphocytes in the graft to host antigens) in bone marrow transplants
  - —to treat a variety of conditions that, while not completely understood, are believed to have an important autoimmune component in their pathogenesis: idiopathic thrombocytopenic purpura, some forms of haemolytic anaemia, some forms of of glomerulonephritis, myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis, psoriasis and ulcerative colitis.
- Therapy for this third category often involves a combination of glucocorticoid and cytotoxic agents.
- For transplantation of organs or bone marrow, ciclosporin is usually combined with a glucocorticoid, a cytotoxic drug or an antilymphocyte immunoglobulin.

Immunosuppressants

- Clonal proliferation of Th cells can be decreased through inhibition of transcription of interleukin-2: ciclosporin, tacrolimus and glucocorticoids act in this way
  —ciclosporin and tacrolimus are given orally or i.v.; common adverse effect is nephrotoxicity

- DNA sythesis is inhibited by:
  —azathioprine through its active metabolite mercaptopurine
  —mycophenolate mofetil through inhibition of de novo purine synthesis.
- T cell signal transduction events are blocked by basiliximab and daclizumab, which are monoclonal antibodies against the α-chain of the interleukin-2 receptor.

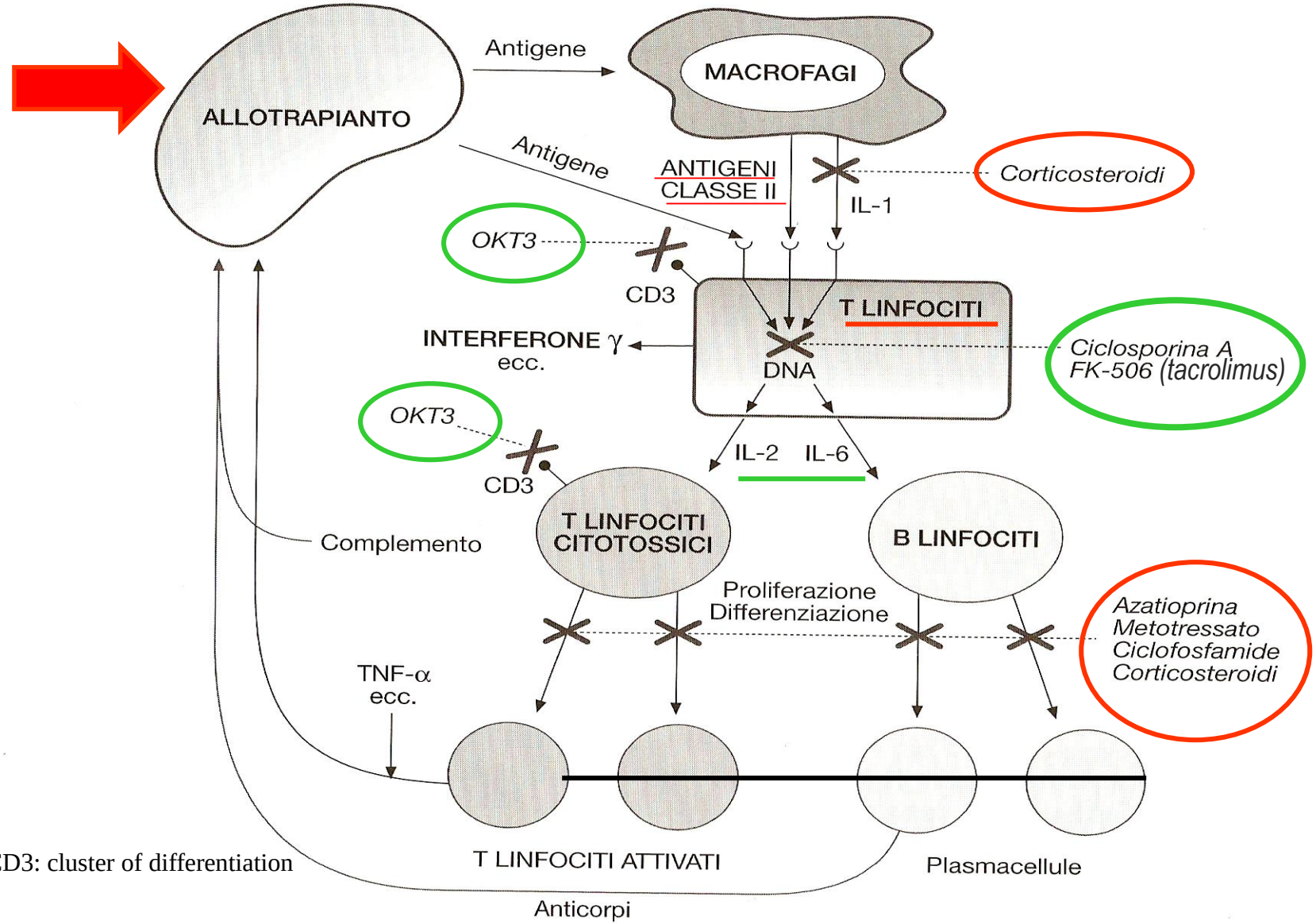
Immunosuppressant drugs

Agente farmacologico	Bersaglio metabolico	Effetto principale
Ciclofosfamide	Alchilazione del DNA	Blocco della sintesi del DNA
Metotressato	Diidrofolato reduttasi	»
Azatioprina	Sintesi della purine	»
Micofenolato mofetile	Deidrogenasi IMP	»
Brequinar	Deidrogenasi diidrorato	»
15-Desossispergualina	Sconosciuto	Immunosoppressione
Corticosteroidi	Recettore per gli steroidi	Inibizione della sintesi di citochine
Anticorpi monoclonali anti-TCR, OKT3	Complesso TCR/CD3	Blocco dell'attivazione dei linfociti e deplezione linfocitaria
Anticorpi monoclonali anti-CD4	CD4	
* Anticorpi monoclonali anti-IL-2	Recettore per la IL-2	»
Ciclosporina A	Calcineurina	Blocco della attivazione dei linfociti ed effetto antiinfiammatorio
FK-506 (tacrolimus)	Calcineurina	
Rapamicina	$p70^{S6k}$, $p33^{cdk2}$ e $p34^{cdc2}$	Blocco della attivazione dei linfociti
IL-10	Produzione delle citochine	»

* Basilimax, daclizumab = antibody IL2

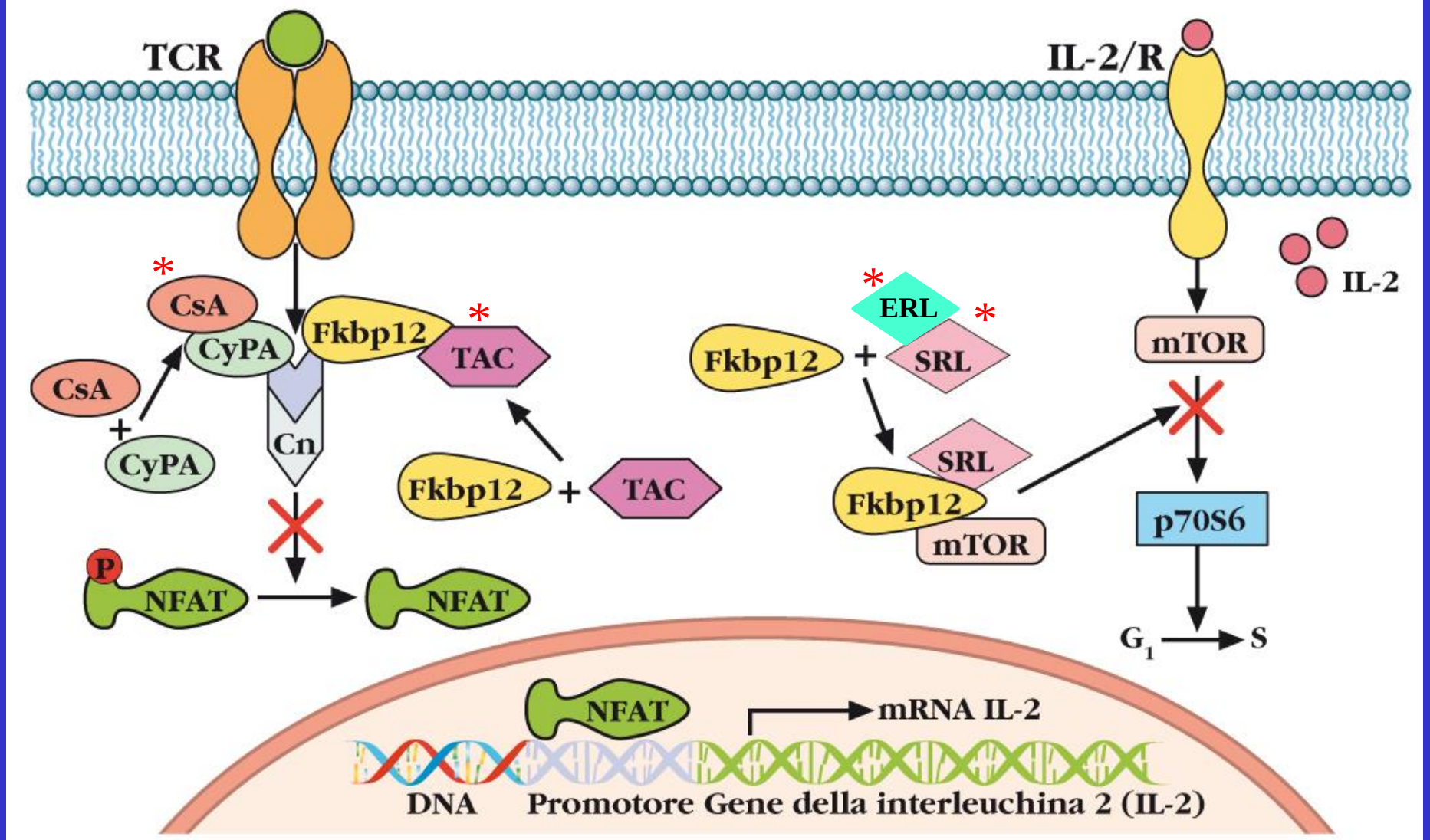
Side Effects

	Glucocorticoidi	Ciclosporina A	Tacrolimus	Sirolimus	Azatioprina	Acido Micofenolico
Potenza	+	+++	++++	+++	+	++
Nefrotossicità	-	++	++	-	-	-
Neurotossicità	-	+	++	-	-	-
Irsutismo	++	++	-	-	-	-
Rash cutaneo	-	-	-	+	-	-
Diabete	++	+	++	-	-	-
Diarrea	-	-	-	+	-	++
Epatotossicità	-	+	+	+	+	-
Mielosopressione	-	-	+	+	+	+



CD3: cluster of differentiation

Fig. 9.4. Meccanismi immunologici fondamentali della risposta antigenica all'allotrapianto e possibili siti di intervento farmacologico. Gli immunosoppressori aspecifici come i corticosteroidi interferiscono con la sintesi di IL-1 da parte dei macrofagici che presentano l'antigene ai T linfociti; inoltre i corticosteroidi inibiscono la proliferazione dei B e dei T linfociti. Altri immunosoppressori aspecifici (ciclofosfamide, azatioprina e metotressato) inibiscono la proliferazione e la differenziazione dei B e T linfociti. Viceversa, gli immunosoppressori specifici come la CsA ed il composto FK-506 interferiscono con i meccanismi molecolari che controllano a livello del DNA la sintesi di citochine (IL-2, IL-6, ecc.) che inducono la proliferazione dei T linfociti *helper*. Altri meccanismi di immunosoppressione specifica possono essere realizzati con anticorpi monoclonali (OKT3) diretti contro la molecola CD3 dei linfociti umani.



CsA = ciclosporin
TAC = tracrolimus
SRL = sirolimus
ERL = everolimus

Cn = calcineurine (phosphatase)
mTOR = kinase (mamalian target rapamicine)
NF-AT = activator nuclear factors of T linfocits (IL2)
P70S6 = protein kinase
CyPA, Fkbp12 = immunophylline

Factors interfering with Ciclosporin absorption

- Bioavailability increases with progression of therapy
- Children can bear proportionally higher doses than adults
- Patients with liver transplant having diarrhea have impaired absorption
- Food influences absorption: eg grapefruit increases cyclosporin and tacrolimus concentration

Pharmacological interactions with Ciclosporin (CsA)

DRUGS THAT:
Fenitoina o fenobarbital Carbamazepina Isoniazide Rifampicina Trimethoprim/sulfametossazolo per uso endovenoso	Decrease CsA concentration
Ketoconazolo Eritromicina Steroidi Metilprednisolone Diltiazem Verapamil	Increase CsA concentration
Aminoglicosidici Melfalan Anfotericina 3 Trimethoprim/sulfametossazolo Trimethoprim	Reduce renal function

St. John's wort
(Hypericum perforatum)

Mechanism of action

MAO inhibition, reuptake inhibition 5HT, NA, DA, GABA, Glu

Collateral mechanisms

P-glycoprotein substrate (transfer: absorption, elimination, distribution and extrudes drugs from cells) and activity induction (intestine, kidney, liver, testicles brain, blood tissues)

CYP3A4 and CPY1A2 induction

Interactions

ciclosporine

digossine

teophilline

indinavir

warfarine

amitriptiline

contraceptivess

paroxetine

Tocilizumab (monoclonal antibody)

Treatment of patients with **rheumatoid arthritis** (RA).
Studied as a treatment for **Crohn's disease** and systemic **lupus erythematosus**