GLUCOCORTICOIDS
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 glicocorticoïdri 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 glicocorticoïdri sono in grado di controllare l’attivazione dell’asse ipotalamo-ipofisi-surrene e quindi la propria sintesi.
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)
Glucocorticoids

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.
Mechanism of action of glucocorticoids

Coactivators:
SRC (steroid),
GRIP (glucocorticoid),
CBP (cAMP)
<table>
<thead>
<tr>
<th>Inibizione della sintesi di proteine proinfiammatorie ed immunostimolanti</th>
<th>Induzione della sintesi di proteine antinfiammatorie ed immunodepressive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Citochine e recettori</strong></td>
<td><strong>Annessina-1</strong></td>
</tr>
<tr>
<td>IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-12</td>
<td>Recettore di tipo II per IL-1</td>
</tr>
<tr>
<td>TNFα, IFNγ</td>
<td>IkBa</td>
</tr>
<tr>
<td>Recettori per IL-2</td>
<td>GILZ</td>
</tr>
<tr>
<td>Chemochine</td>
<td>MAPK fosfatasi-1</td>
</tr>
<tr>
<td>IL-8</td>
<td></td>
</tr>
<tr>
<td>MCP-1</td>
<td></td>
</tr>
<tr>
<td><strong>Fattori di crescita</strong></td>
<td></td>
</tr>
<tr>
<td>GM-CSF</td>
<td></td>
</tr>
<tr>
<td>G-CSF</td>
<td></td>
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<tr>
<td><strong>Molecole di adesione</strong></td>
<td></td>
</tr>
<tr>
<td>E-selectin</td>
<td></td>
</tr>
<tr>
<td>ELAM-1</td>
<td></td>
</tr>
<tr>
<td>ICAM-1</td>
<td></td>
</tr>
<tr>
<td><strong>Enzimi</strong></td>
<td></td>
</tr>
<tr>
<td>Fosfolipasi A2</td>
<td></td>
</tr>
<tr>
<td>Cicloossigenasi inducibile</td>
<td></td>
</tr>
<tr>
<td>Nitrossidosintasi inducibile</td>
<td></td>
</tr>
<tr>
<td>Collagenasi</td>
<td></td>
</tr>
<tr>
<td>Metalloproteinasi</td>
<td></td>
</tr>
</tbody>
</table>

- 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 cyclooxygenase-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.
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.
Mineralocorticoid Activity

Renin-angiotensin-aldosterone system

Decrease in renal perfusion (juxtaglomerular apparatus) leads to the release of renin from the kidneys. Renin converts angiotensinogen to angiotensin I, which is further converted to angiotensin II by ACE (angiotensin-converting enzyme) in the lungs. Angiotensin II stimulates aldosterone secretion from the adrenal cortex, leading to increased reabsorption of sodium and chloride ions and increased potassium excretion. This results in water retention and an increase in blood pressure. ADH (antidiuretic hormone) is also released, increasing water reabsorption in the collecting ducts.

Legend:
- Blue line: secretion from an organ
- Red line with plus: stimulatory signal
- Red line with minus: inhibitory signal
- Black line: reaction
- Gray line: active transport
- Dashed line: passive transport

Water and salt retention. Effective circulating volume increases. Perfusion of the juxtaglomerular apparatus increases.
CORTICOSTEROID DRUGS
<table>
<thead>
<tr>
<th>Compound</th>
<th>Relative affinity for glucocorticoid receptors&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Approximate relative potency in clinical use</th>
<th>Duration of action after oral dose&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone (cortisol)</td>
<td>1</td>
<td>Anti-inflammatory 1</td>
<td>Sodium retaining 1</td>
<td>Short</td>
</tr>
<tr>
<td>Cortisone</td>
<td>0.01</td>
<td>0.8</td>
<td>0.8</td>
<td>Short</td>
</tr>
<tr>
<td>Corticosterone</td>
<td>0.85</td>
<td>0.3</td>
<td>15</td>
<td>Short</td>
</tr>
<tr>
<td>Prednisolone *</td>
<td>2.2</td>
<td>4</td>
<td>0.8</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Prednisone</td>
<td>0.05</td>
<td>4</td>
<td>0.8</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Methylprednisolone*11.9</td>
<td>11.9</td>
<td>5</td>
<td>Minimal</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>1.9</td>
<td>5</td>
<td>None</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Dexamethasone *</td>
<td>7.1</td>
<td>30</td>
<td>Minimal</td>
<td>Long</td>
</tr>
<tr>
<td>Betamethasone *</td>
<td>5.4</td>
<td>30</td>
<td>Negligible</td>
<td>Long</td>
</tr>
<tr>
<td>Deoxycortone</td>
<td>0.19</td>
<td>Negligible</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>3.5</td>
<td>15</td>
<td>150</td>
<td>Short</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>0.38</td>
<td>None</td>
<td>500</td>
<td>-</td>
</tr>
</tbody>
</table>
• 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
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 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 synthesis** 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.
# Tab. 9.1. Principali farmaci immunosoppressori attualmente impiegati clinicamente o sperimentalmente.

<table>
<thead>
<tr>
<th>Agente farmacologico</th>
<th>Bersaglio metabolico</th>
<th>Effetto principale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciclofosfamide</td>
<td>Alchilazione del DNA</td>
<td>Blocco della sintesi del DNA</td>
</tr>
<tr>
<td>Metotrexato</td>
<td>Diidrofolato reduttasi</td>
<td>»</td>
</tr>
<tr>
<td>Azatioprina</td>
<td>Sintesi della purine</td>
<td>»</td>
</tr>
<tr>
<td>Micofenolato mofetile</td>
<td>Deidrogenasi IMP</td>
<td>»</td>
</tr>
<tr>
<td>Brequinar</td>
<td>Deidrogenasi diidrato</td>
<td>»</td>
</tr>
<tr>
<td>15-Desossisergualina</td>
<td>Sconosciuto</td>
<td>Immunosoppressione</td>
</tr>
<tr>
<td>Corticosteroidi</td>
<td>Recettore per gli steroidi</td>
<td>Inibizione della sintesi di citochine</td>
</tr>
<tr>
<td><strong>Anticorpi monoclonali anti-TCR, OKT3</strong></td>
<td>Compless TCR/CD3 CD4</td>
<td>Blocco dell’attivazione dei linfociti e deplezione linfocitaria</td>
</tr>
<tr>
<td><strong>Anticorpi monoclonali anti-CD4</strong></td>
<td>Recettore per la IL-2</td>
<td>»</td>
</tr>
<tr>
<td><strong>Anticorpi monoclonali anti-IL-2</strong></td>
<td>Calcineurina</td>
<td>Blocco della attivazione dei linfociti ed effetto antiinflammatorio</td>
</tr>
<tr>
<td>Ciclosporina A</td>
<td>Calcineurina p70S6k, p33cdk2 e p34cdk2</td>
<td>Blocco della attivazione dei linfociti</td>
</tr>
<tr>
<td>FK-506 (tacrolimus)</td>
<td>Produzione delle citochine</td>
<td>»</td>
</tr>
<tr>
<td>Rapamicina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Basilimax, daclizumab = antibody IL2
### Side Effects

<table>
<thead>
<tr>
<th></th>
<th>Glucocorticoidi</th>
<th>Ciclosporina A</th>
<th>Tacrolimus</th>
<th>Sirolimus</th>
<th>Azatioprina</th>
<th>Acido Micofenolico</th>
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<tbody>
<tr>
<td>Potenza</td>
<td>+</td>
<td>+++</td>
<td>++++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Nefrotossicità</td>
<td>-</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Neurotossicità</td>
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<td>++</td>
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<tr>
<td>Irsutismo</td>
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<td>Rash cutaneo</td>
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<td>++</td>
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<tr>
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<td>+</td>
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<td>Mielosoppressione</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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</tbody>
</table>
Fig. 9.4. Meccanismi immunologici fondamentali della risposta antigenica all’allotrasplantato e possibili siti di intervento farmacologico. Gli immunosoppressori aspecifici come i corticosteroidi interferiscono con la sintesi di IL-1 da parte dei macrofagi 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 metotrexato) 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 = ciclosporina
TAC = tracrolimus
SRL = sirolimus
ERL = everolimus

Cn = calcineurine (phosphatase)
mTOR = kinase (mamalian target rapamicine)
NF-AT = activator nuclear factors of T lymphocytes (IL2)
P70S6 = protein kinase
CyPA = ciclophylline

NFAT mRNA IL-2
DNA Promotore Gene della interleuchina 2 (IL-2)
Factors interfering with CsA 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
Tab. 9.3. Possibili interazioni farmacologiche tra CsA ed altri farmaci.

<table>
<thead>
<tr>
<th>Farmaci che possono <strong>diminuire la concentrazione di CsA</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenitoina o fenobarbital</td>
</tr>
<tr>
<td>Carbamazepina</td>
</tr>
<tr>
<td>Isoniazide</td>
</tr>
<tr>
<td>Rifampicina</td>
</tr>
<tr>
<td>Trimethoprim/sulfametossazolo per uso endovenoso</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Farmaci che possono <strong>aumentare la concentrazione di CsA</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazolo</td>
</tr>
<tr>
<td>Eritromicina</td>
</tr>
<tr>
<td>Steroidi</td>
</tr>
<tr>
<td>Metilprednisolone</td>
</tr>
<tr>
<td>Diltiazem</td>
</tr>
<tr>
<td>Verapamil</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Farmaci che possono <strong>ridurre la funzionalità renale</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglicosidici</td>
</tr>
<tr>
<td>Melfalan</td>
</tr>
<tr>
<td>Anfotericina 3</td>
</tr>
<tr>
<td>Trimethoprim/sulfametossazolo</td>
</tr>
<tr>
<td>Trimethoprim</td>
</tr>
</tbody>
</table>

**Altre potenziali interazioni farmacologiche**

Lovastatina
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
- amitriptiliné
- contraceptives
- paroxetine
Tocilizumab (monoclonal antibody)

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