대한천식알레르기학회 광주전남지회 2023년 후반기 학술집담회

Glucocorticoids

Part 1. 알레르기 질환에서 스테로이드 작용 기전과 임상적 활용

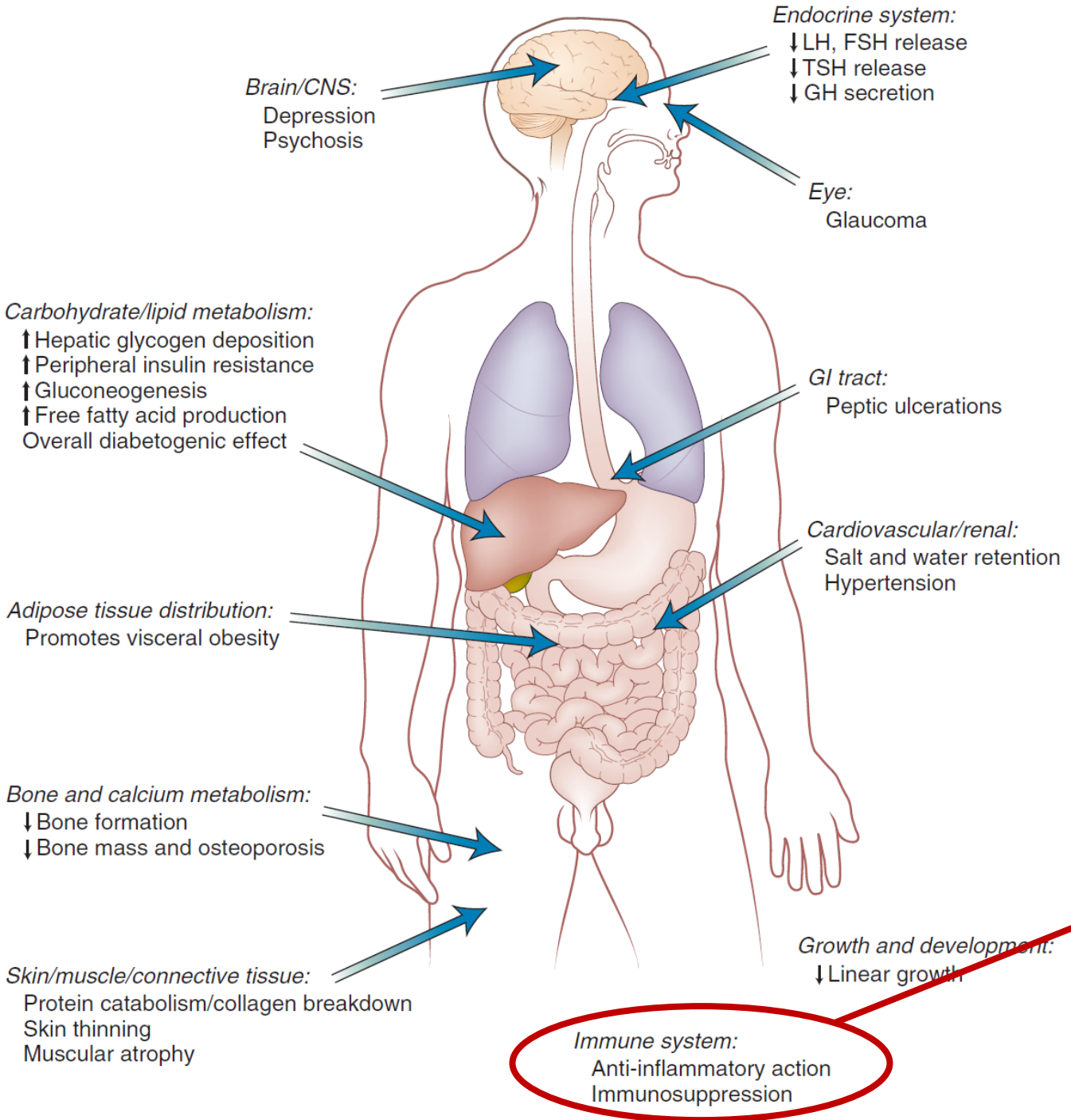
Part 2. 이상반응과 저항

일시: 2023년 8월 29일(화)

장소: 전남대학교병원 의생명연구지원센터 1층 대회의실

연자: 광주속편한내과 권용은

Introduction

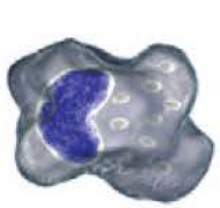


- 가장 일반적으로 처방되는 약물
  광범위한 의학적 상태에 사용

- 일반 인구의 0.5%
  55세 이상 여성의 1.75%
  류마티스 관절염 환자의 56-68%

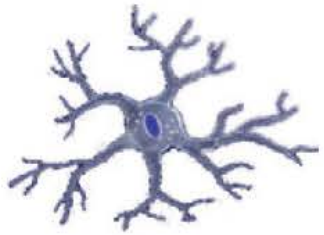
- **알레르기 질환 관점**
  가장 효과적이고 비용 효율적인
  항염증, 항증식,
  면역 조절(억제) 약물

Therapeutic Effects of glucocorticosteroids in asthma



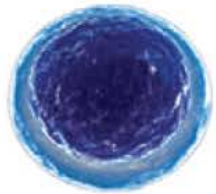
Macrophage

↓ mediators



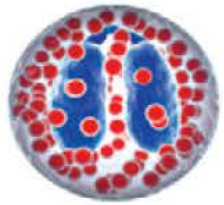
Dendritic cell

inhibit function through inhibition of costimulatory molecules



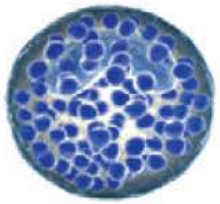
Lymphocyte

↓ mediators



Eosinophil

↓ numbers



Mast cell

Degranulation is not fully inhibited (ex; skin prick test)
Diminish activity, type 2 cytokines production
Reduce expression of chemokines for tissue recruitment,
Impact mast cell location within a tissue

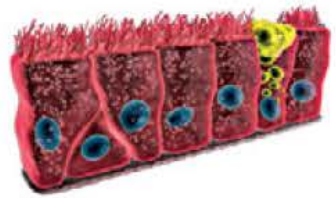
Glucocorticoids

Smooth muscle cells

↑ β_2R expression
↓ remodelling?

Capillary endothelium

↓ microvascular leak
↓ angiogenesis



Respiratory epithelial cells, goblet cell

↓ mediators
↓ mucus secretion tight junction remodelling

History

THE USE OF ADRENAL SUBSTANCE IN THE TREATMENT OF ASTHMA.

BY SOLOMON SOLIS-COHEN, M.D.

Professor of Medicine and Therapeutics in the Philadelphia Polyclinic; Clinical-Lecturer on Medicine, Jefferson Medical College; Physician to the Philadelphia and Rush Hospitals; Consulting Physician to the Jewish Hospital, etc.

PHILADELPHIA.

The experience I have to submit in the use of adrenal substance in this particular connection, is of but little importance, except as a link in a chain of studies.

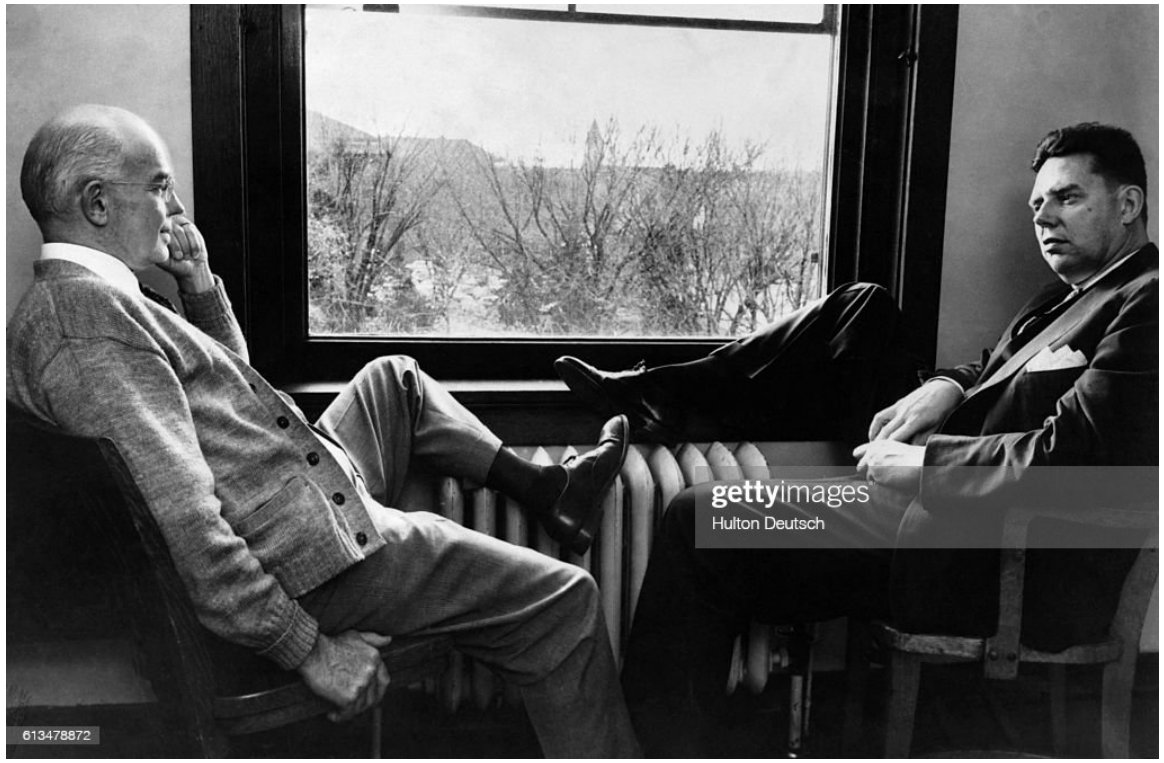
The synthesis of disease—i. e., the manner in which syndrome groups are built up, and the reason of their association—is beginning to attract the attention of students who recognize that pathology is something more than morbid anatomy or bacteriology.

REPRINTED FROM
THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION
MAY 12, 1900

Dr. Solomon Solis-Cohen (1857-1948)

Epinephrine < Glucocorticoid

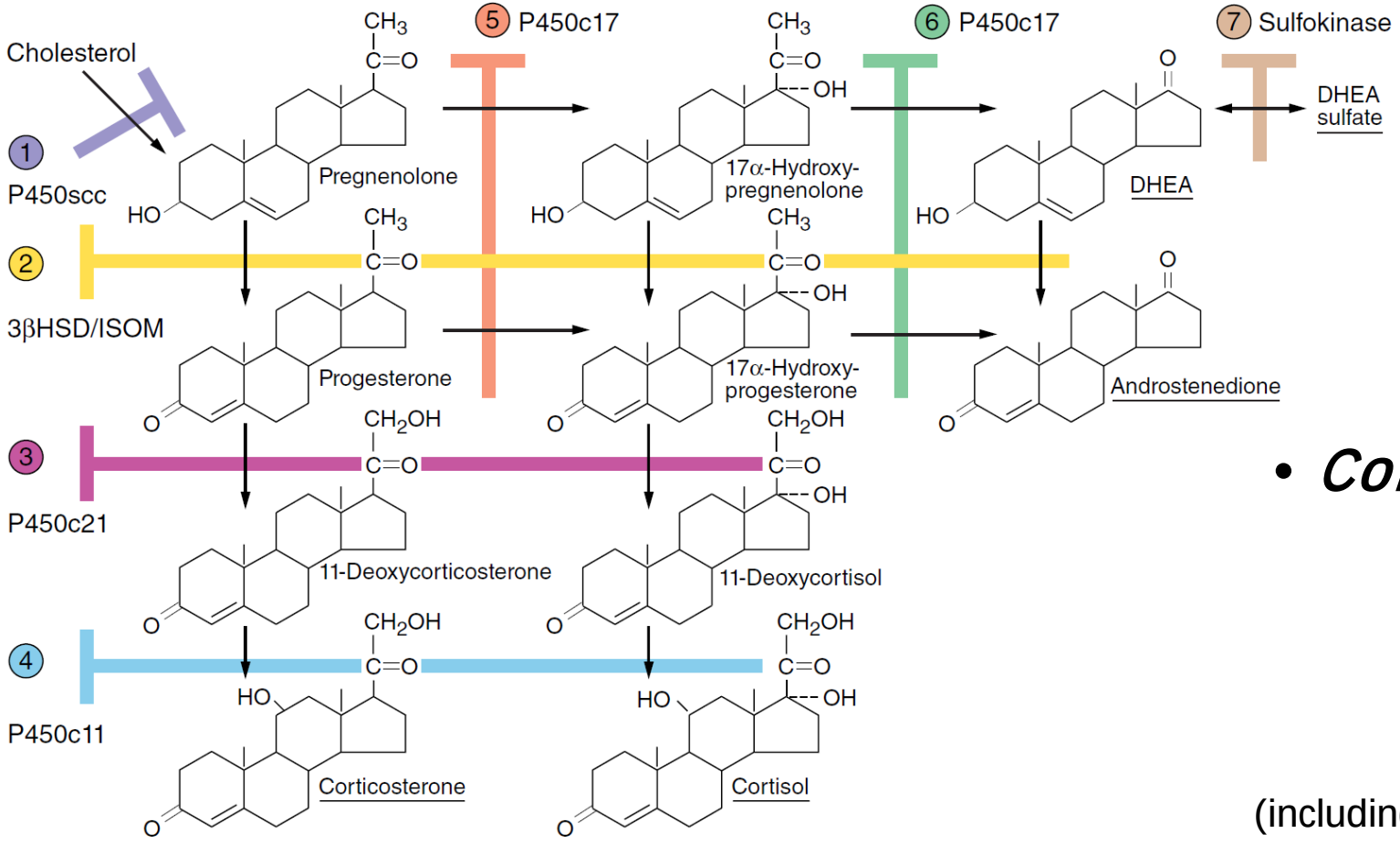
History



Edward C. Kendall (l) and Phillip S. Hench,
who shared the 1950 Nobel Prize for Medicine
for their research into hormones(cortisone, ACTH)

JOHN E. BORDLEY
First demonstrated the beneficial effect of ACTH in treating allergic disease (1949)

Terminology



- ***Glucocorticoid*(GC)**
  or *glucocorticosteroid*

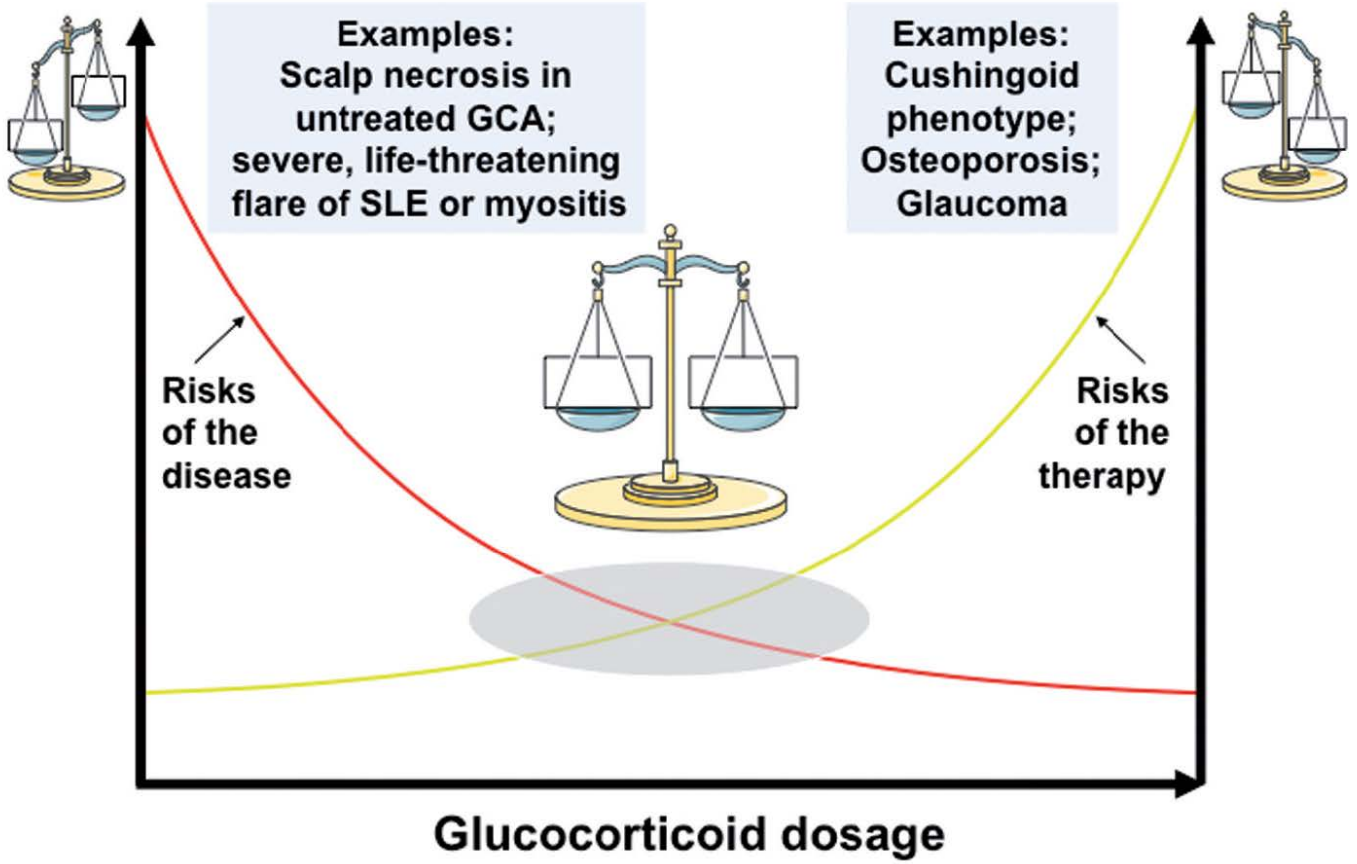
- ***Corticosteroid* or *corticoid***
  ; adrenal cortex synthesizes

- ***Steroid***
  ; chemical compounds characterized by a common multiple-ring structure (including cholesterol, vitamin D, sex hormones)

Modified with permission from Ganong WF. *Review of Medical Physiology*. 16th ed. McGraw-Hill; 1993

Glucocorticoid therapy: a balance of risks

Glucocorticoid 투여량은 치료 중인 질병의
임상 활동 및 중증도와 병행하여 증가



GCA: giant cell arteritis;
SLE: systemic lupus erythematosus;
Grey area: optimal use of glucocorticoids.

Clin Exp Rheumatol 2015; 33 (Suppl. 92): S29-S33

Mechanisms of the Cellular Action of Glucocorticoids (GCs)

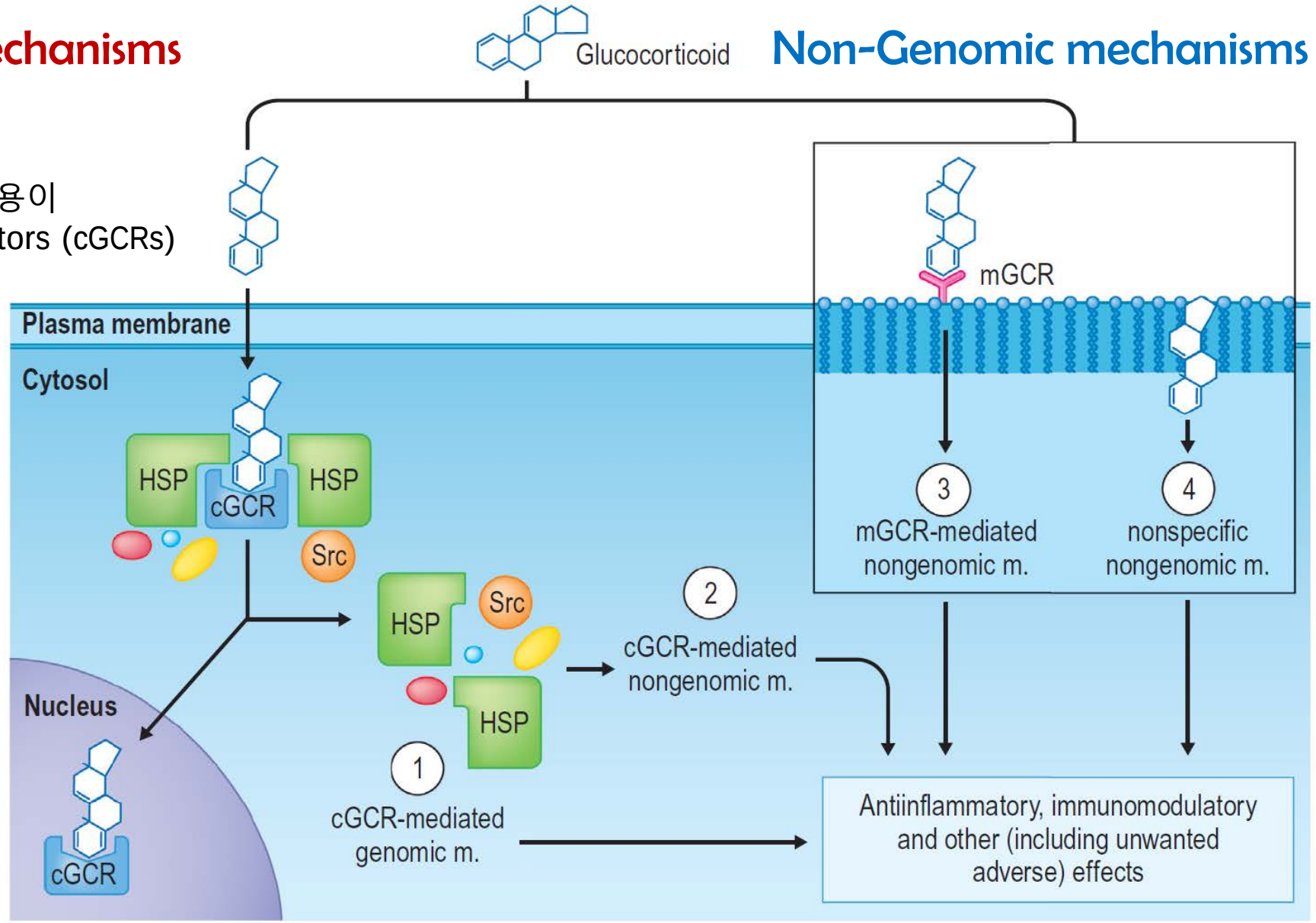
Genomic mechanisms

- **지질친화, 저용량 구조** -세포막 투과 용이
- Bind to cytosolic glucocorticoid receptors (cGCRs)

GC/cGCR 복합체 핵 내로 이동
(20분 정도 소요)

GC/cGCR 복합체는
DNA와 결합되어 작용

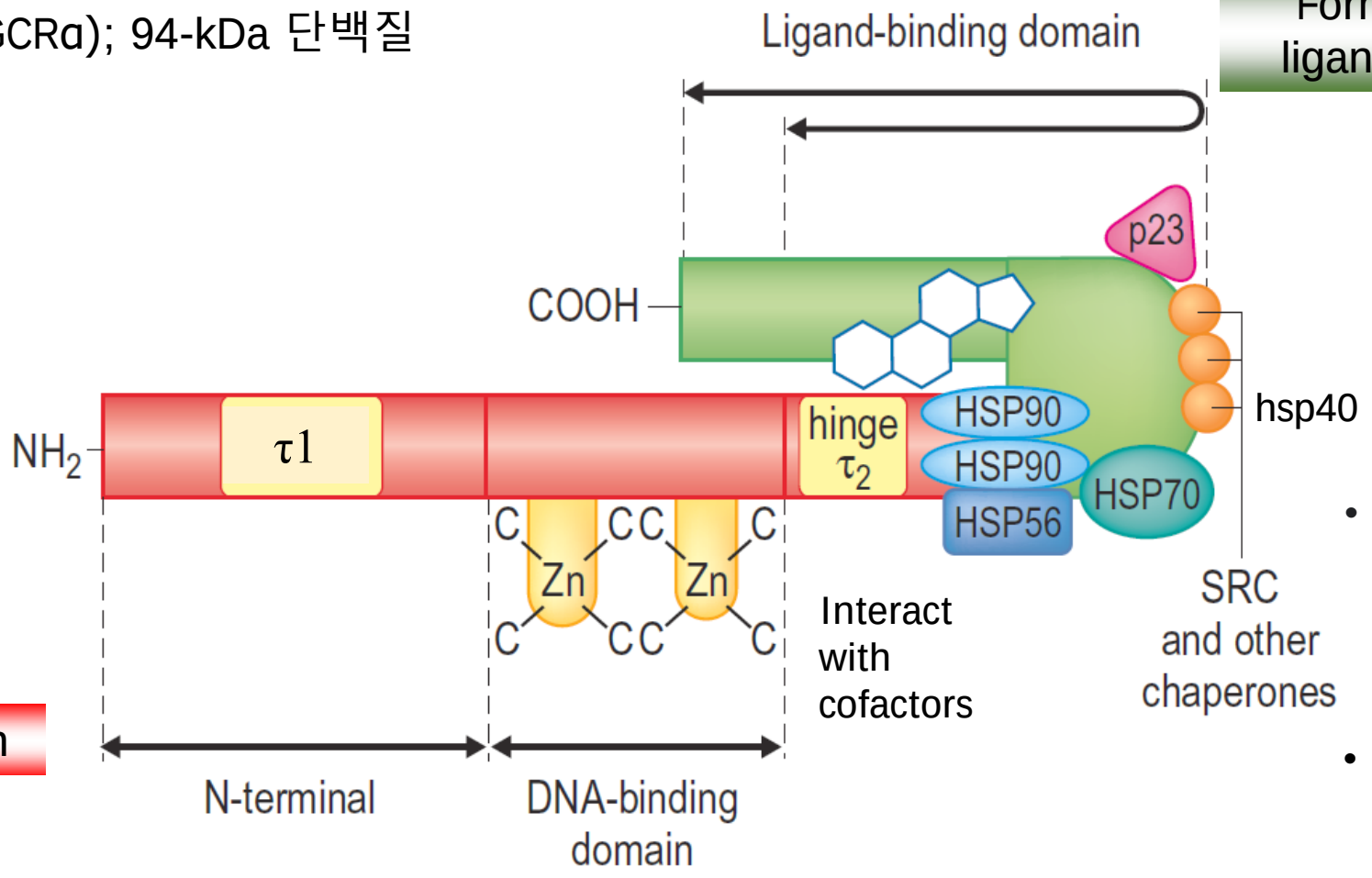
Non-Genomic mechanisms



Structure of the Cytosolic Glucocorticoid Receptor(cGCR)

비활성화 cGCR (cGCRα); 94-kDa 단백질

Form a hydrophobic ligand-binding pocket



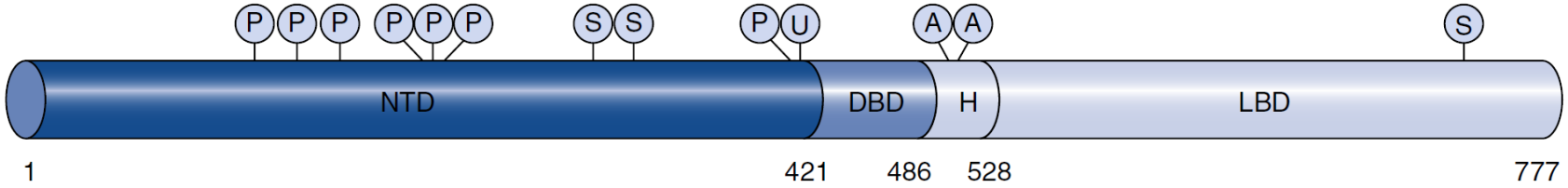
Serves transactivation

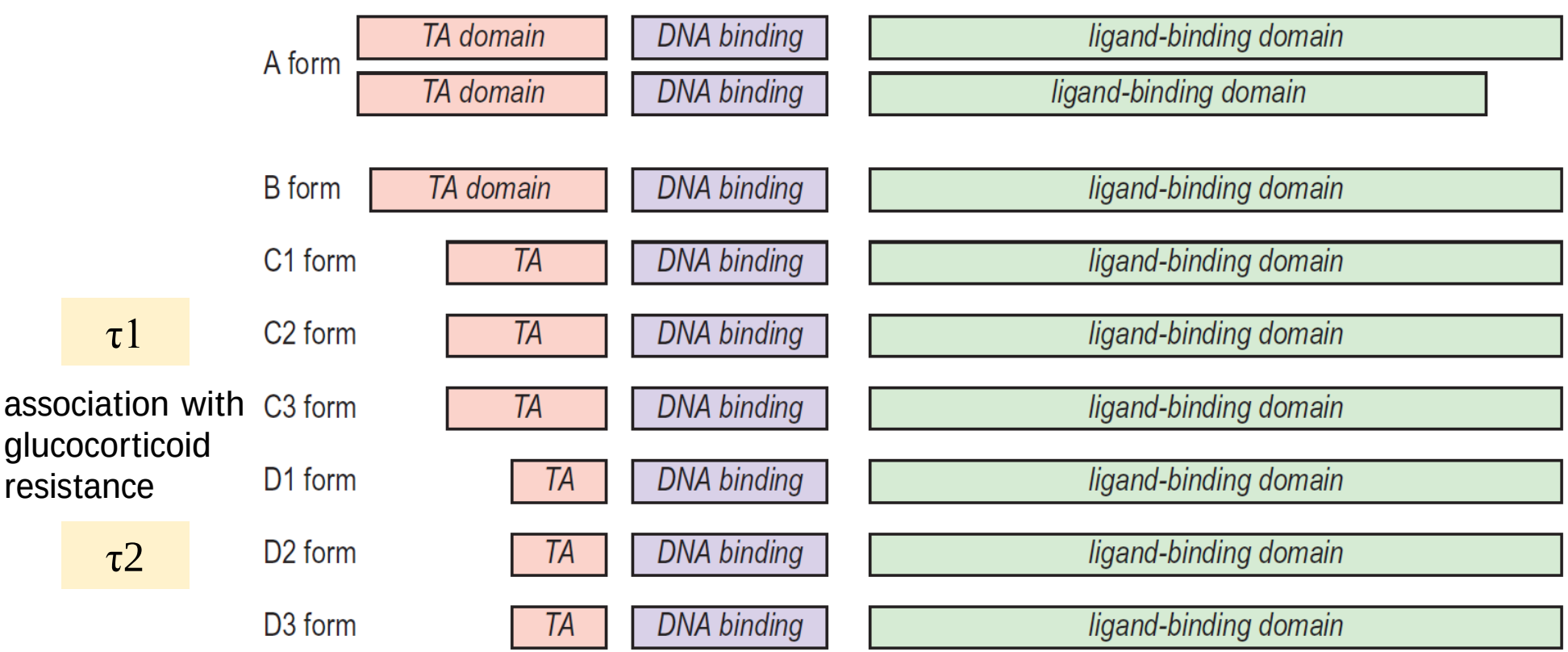
- 접힘, 조립, 전위 및 분해의 중간 단계에서 단백질을 결합하고 안정화
- 세포 내 신호 전달 조절

HSP; heat shock proteins

From Buttgereit F, StraubRH, Wehling M, Burmester GR. Glucocorticoids in the treatment of rheumatic diseases. An update on mechanisms of action. Arthritis Rheum 2004;50:3408–17

Modular structure of the glucocorticosteroid receptor (GR)





GR-α

GR-β

- GC와 결합하지 않음
- 주로 핵 내에서 발견
- GCR-α 매개 유전자 활성화 억제
- 중증 천식, 야간 천식 환자에서 GR-β 발현 증가 관찰

τ1

association with glucocorticoid resistance

τ2

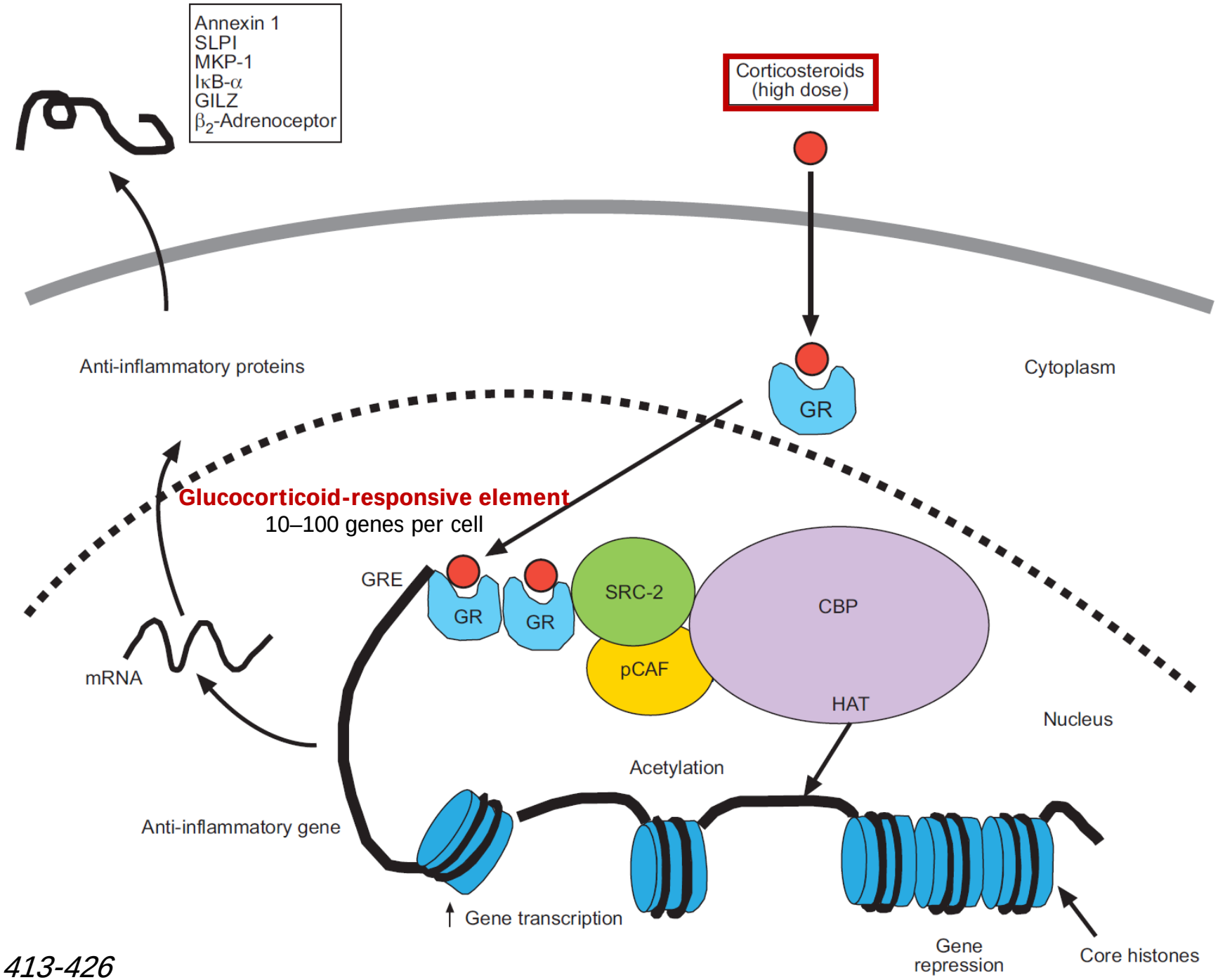
NTD; N-terminal transactivation domain, H: hinge

Middletons allergy principles and practice 8th figure 99-4

Increased transcription (trans-activation)

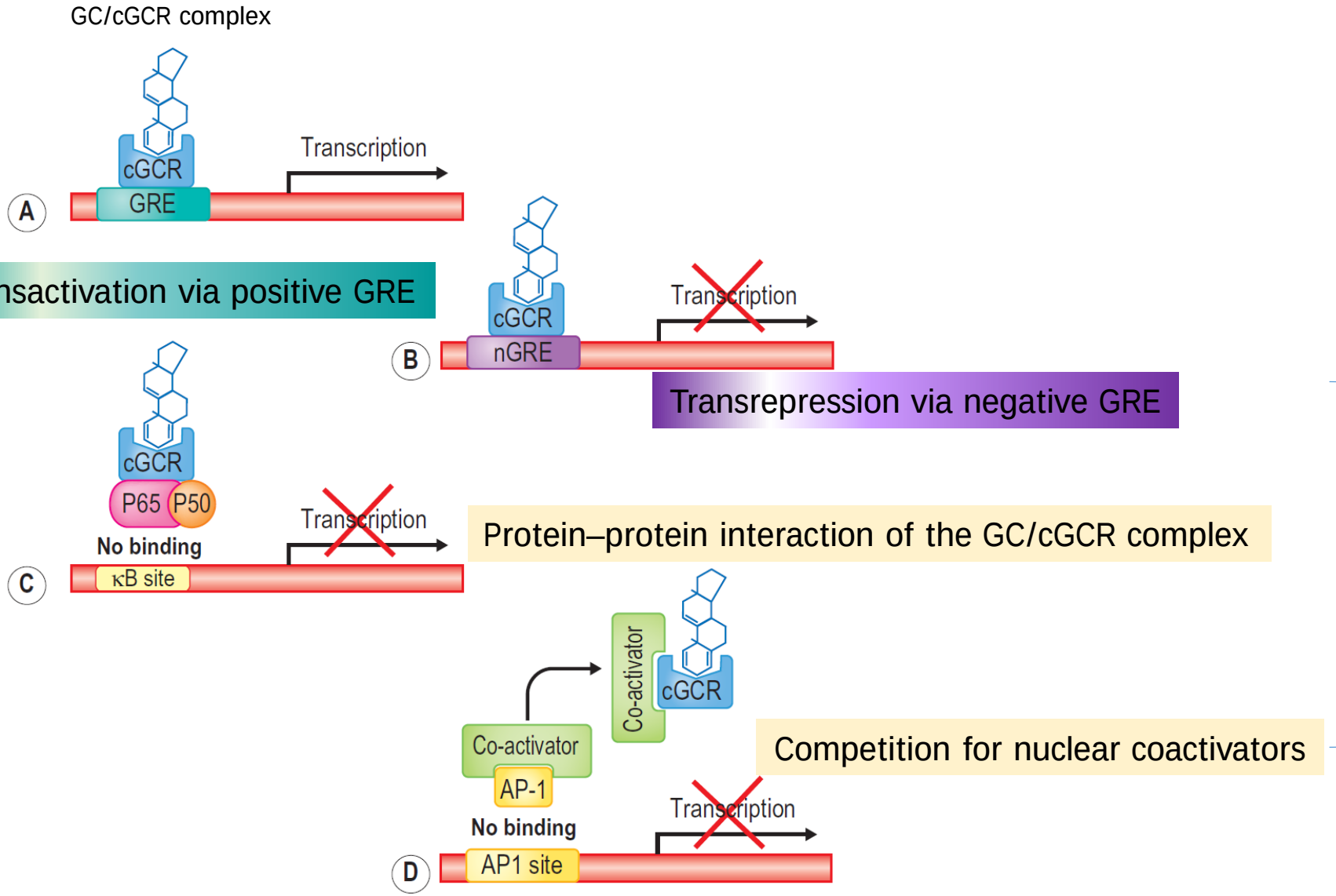
secretory leukoprotease inhibitor (SLPI)
mitogen-activated protein kinase phosphatase (MKP)-1
inhibitor of nuclear factor-kB (IkB-a)
glucocorticoid-induced leucine zipper protein (GILZ)
Phospholipase A2 inhibitor (CC10)
IL-1 receptor antagonist
IL-1 receptor type 2
IL-10(indirectly)

Corticosteroid activation of anti-inflammatory gene expression



European Respiratory Journal 2006 27: 413-426

Genomic Mechanisms of Glucocorticoids (GCs)

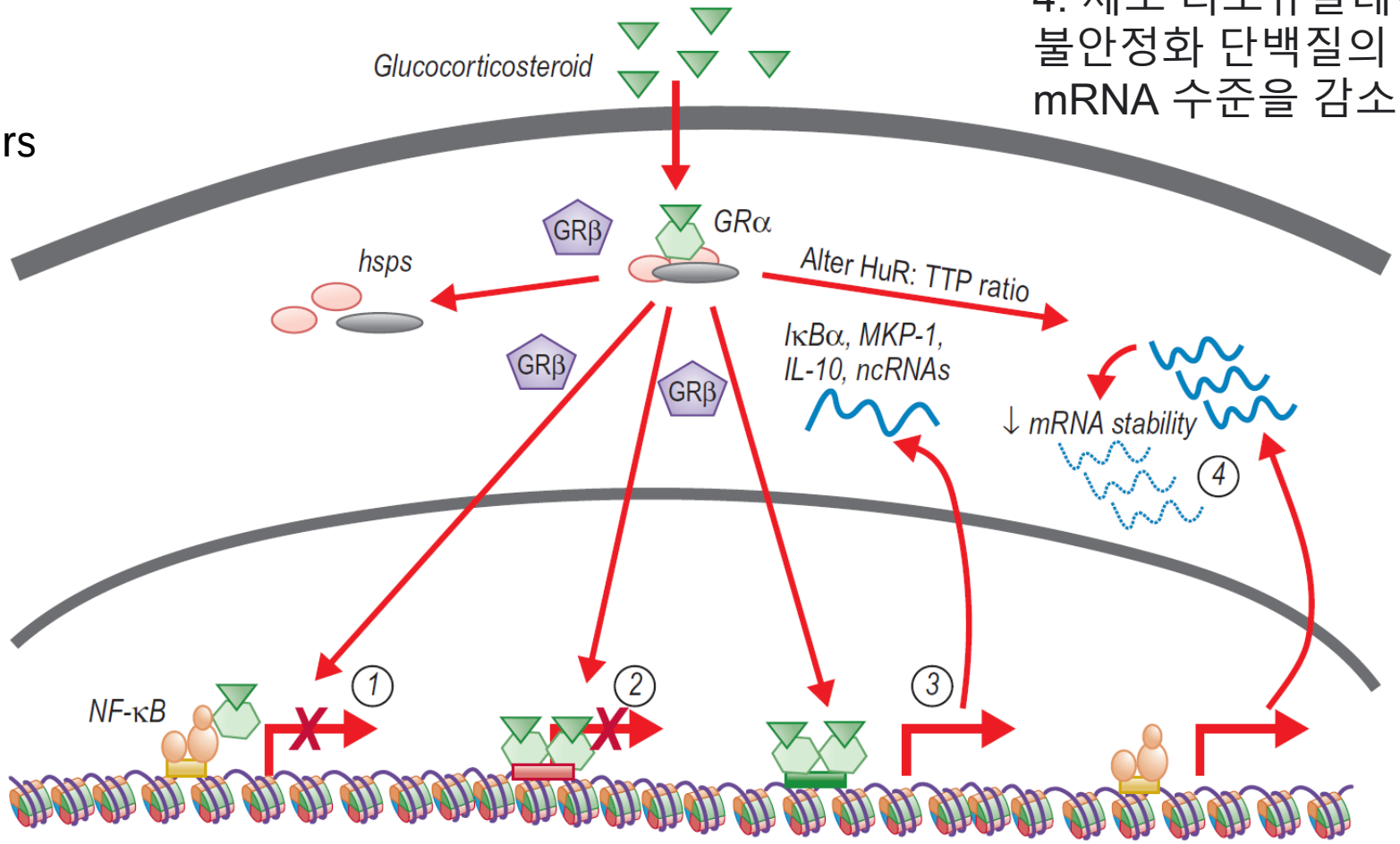


Translation/synthesis of specific regulator proteins

Inhibition of expression of many immunoregulatory and inflammatory cytokines

Mechanisms of glucocorticosteroid receptor (GR) action

Prevented by inhibitors
- transcription ;actinomycin D
- Translation; cycloheximide



4. 세포 리보뉴클레아제 및 mRNA 불안정화 단백질의 수준을 증가시켜 mRNA 수준을 감소

Hu antigen R (HuR) ;mRNA stabilizer

Tristetrapolin (TTP) ;promote mRNA decay

1.Protein–protein interaction of the GC/cGCR complex

2. Transrepression via negative GRE

3. Transactivation via positive GRE

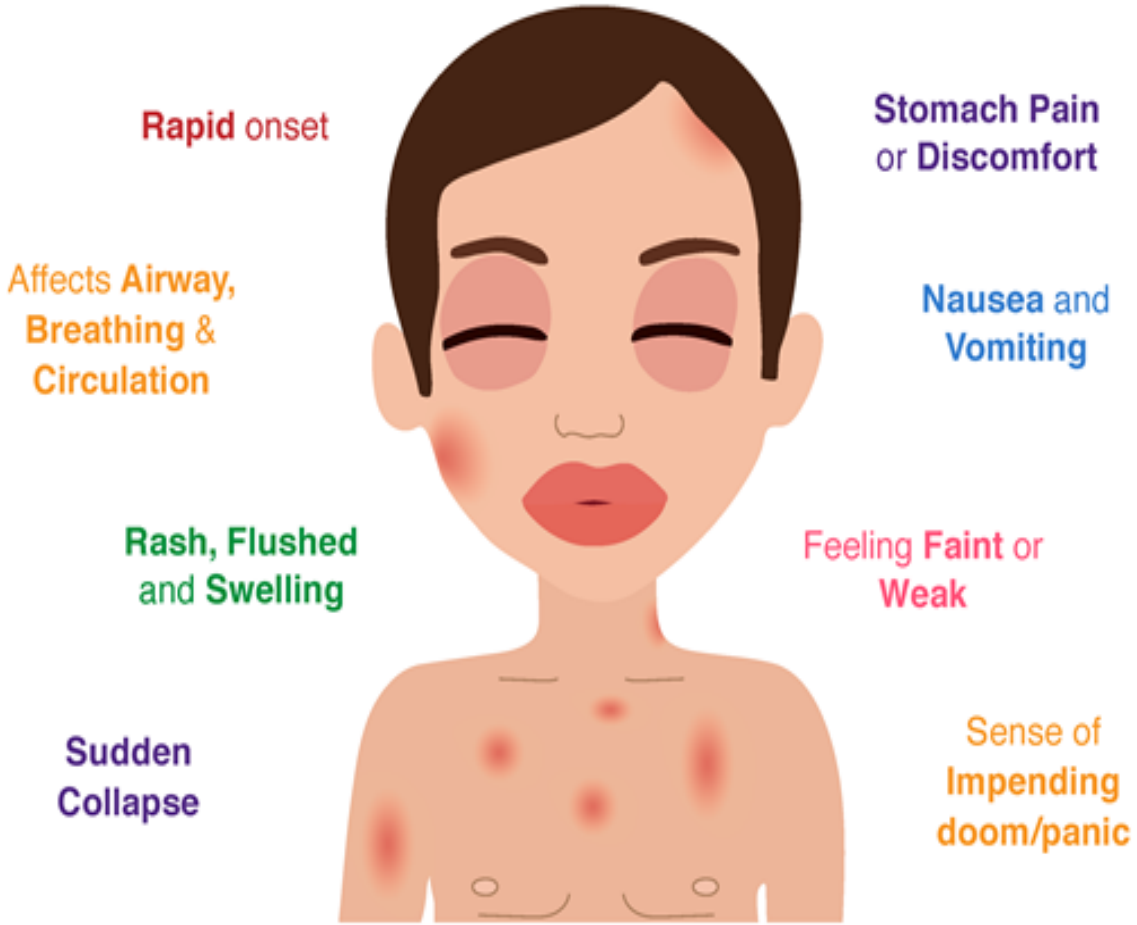
Middletons allergy principles and practice 8th figure 99-4

Characteristics Applying to Genomic Actions

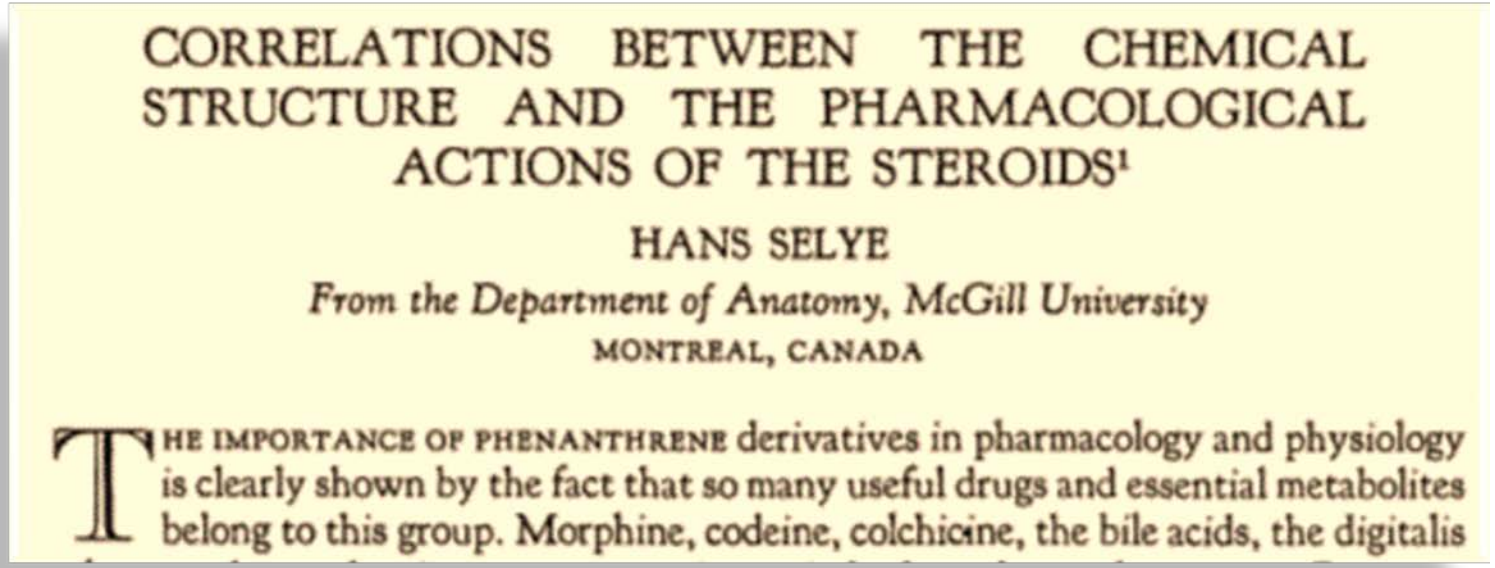
- **생리학적** 기전
- **모든 용량**에서 치료 효과 발생,
  - 미량 - maintenance dose
  - 용량에 따라 GR 포화도 증가 – plateau in 1.0 mg/kg of PDS
- 작용 발현 시간이 **느리다**
  - 조절 단백질 농도의 현저한 변화는 30분 이내에 나타나지 않는다
  - 세포질 글루코코르티코이드 수용체(cGCR) 활성화/전위,
    RNA 전사 및 단백질 변환에 필요한 시간 때문
  - **임상적 효과는 4~6시간 후 발생**

Glucocorticoid Actions; stress hormone

신속한 반응이 요구됨 ⇨ **Genomic action으로 가능할까?**

Basal Levels	*Stress Levels*
	Suppression of CRH, ACTH, ADH, endorphin, POMC
	Insulin antagonism, hyperglycemia, increased liver glycogen
	Cardiovascular changes, increased BP and muscle contractility
	Immunosuppression, lympholysis, altered lymphocyte traffic, anti-inflammatory effects, suppression of cytokines, lymphokines, prostaglandins, etc.
	Induction of glutamine synthetase, tryptophan oxygenase, tyrosine aminotransferase, metallothionein
	Protection against severe stress
	Activation of central nervous system

Rapid Nongenomic Effects of CS



CORRELATIONS BETWEEN THE CHEMICAL STRUCTURE AND THE PHARMACOLOGICAL ACTIONS OF THE STEROIDS[1]

HANS SELYE

From the Department of Anatomy, McGill University

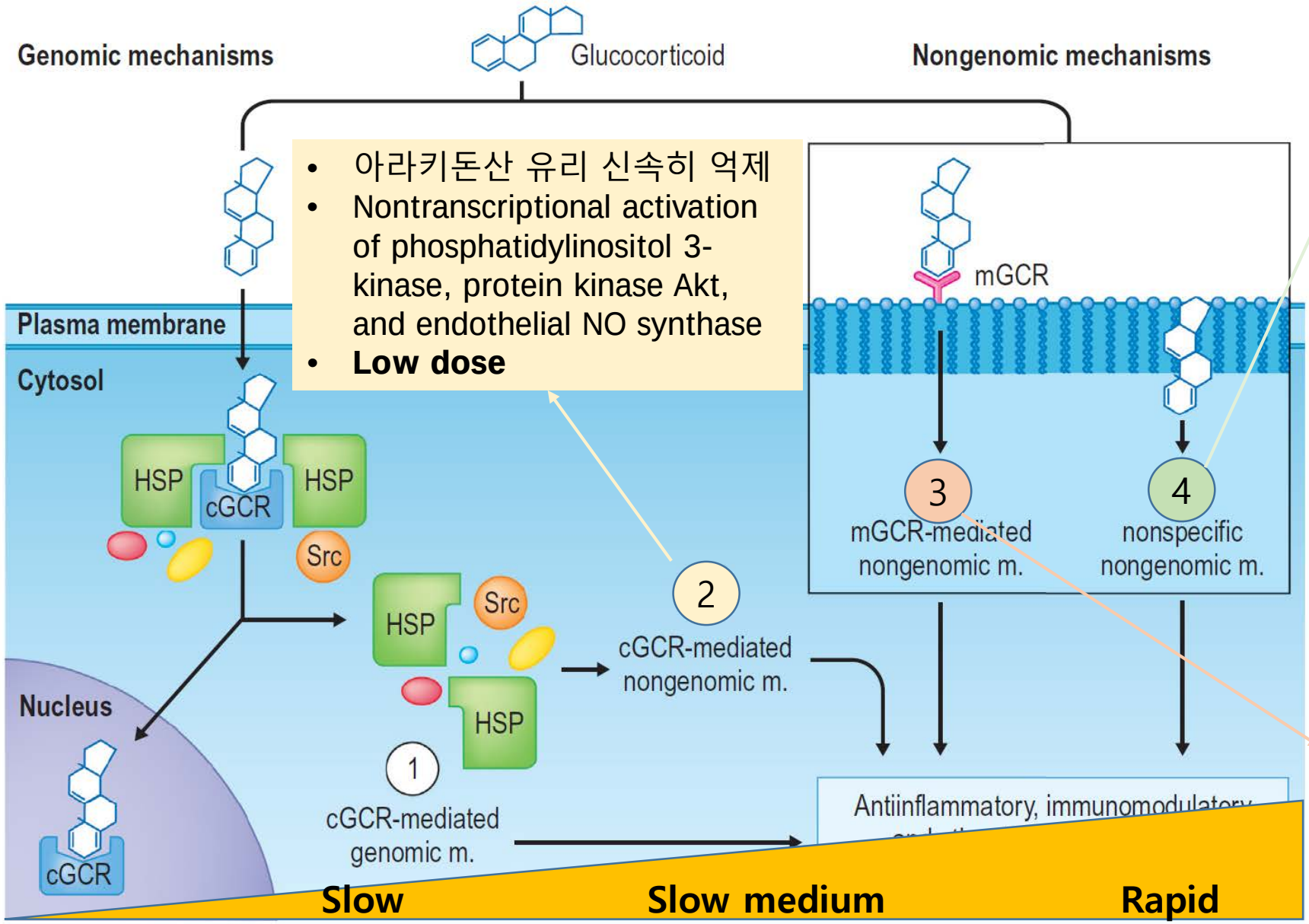
MONTREAL, CANADA

THE IMPORTANCE OF PHENANTHRENE derivatives in pharmacology and physiology is clearly shown by the fact that so many useful drugs and essential metabolites belong to this group. Morphine, codeine, colchicine, the bile acids, the digitalis

- 실제 임상 치료에 활용
- 수 분 이내에 임상 효과 발현
- First notification of a nongenomic effect of CS. (in 1948)

- *Under stress conditions, the GC concentration in the blood can rise to reach up to ten times its basal level.*
- *During the stress response, therefore, the GC concentration may reach levels required for nongenomic effects*

Nongenomic Actions of Glucocorticoids



- 아라키돈산 유리 신속히 억제
- Nontranscriptional activation of phosphatidylinositol 3-kinase, protein kinase Akt, and endothelial NO synthase
- **Low dose**

- 세포막/미토콘드리아막 물리화학적 상호작용
- 양이온 수송에 영향, 미토콘드리아 양성자 누출을 증가 ⇨세포 기능을 변경
- 면역 세포의 원형질막을 가로지르는 칼슘 및 나트륨 순환 억제
- 신속한 면역 억제 및 염증 감소
- **Very high, pulse therapy**

일부 조절 효과는
수 초 ~수 분 이내에 발생

- Membrane-bound glucocorticoid receptors (mGCRs), variants of cGCR
- PBMCs; monocytes and B cells
- 면역 자극 후 능동적으로 상향 조절 (correlated with disease activity?)
- Unclear in pathogenesis
- Negative feedback regulation

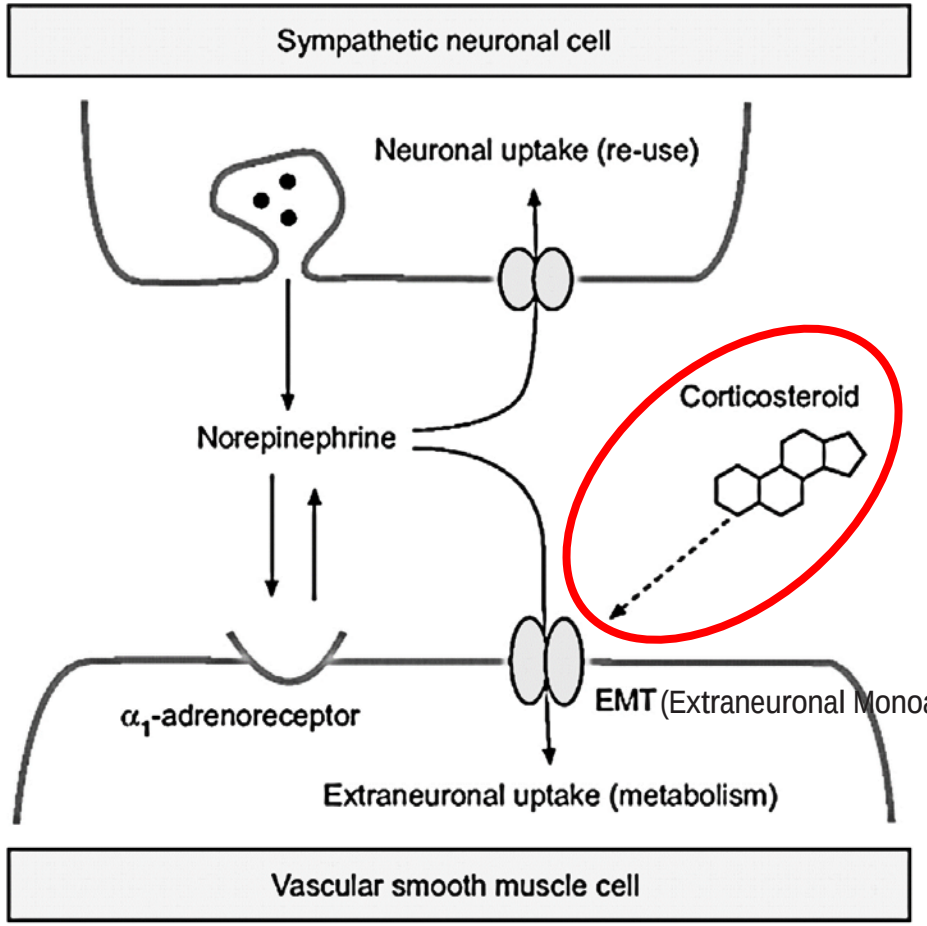
Examples of Various Cell Types Where GCs Were Reported to Have Non-genomic Effects

Signaling pathway(s)	Cell type	GC(s)
PKA SERCA Ca^{2+}-ATPases Adenylyl cyclase	Human bronchial epithelial cells	Dexamethasone
PKC	Mouse cortical collecting duct cells	Dexamethasone Aldosterone
IP3 accumulation PKC	Rat vascular smooth muscle cells	Dexamethasone Aldosterone
PKA	HT4 neuroblastoma cells	Corticosterone
PKC	Rat B103 neuroblastoma cells	Corticosterone
CaMKII AMPK	Mouse skeletal myotubes	Dexamethasone
PKC	Tracheal smooth muscle tissues	Cortisol
Rho kinase	Rat vascular smooth muscle cells	Dexamethasone
ROS/RNS (NO synthase)	Human breast cancer cells	Cortisol
NO pathways	Guinea pig cochlear spiral ganglion neurons Human vascular endothelial cells Human umbilical endothelial cells	Dexamethasone
ERK1/2, p38 MAPK, JNK	PC12 cells Rat vascular smooth muscle cells	Dexamethasone
Src tyrosine kinase	Human breast cancer cells A549 cells	Cortisol Dexamethasone
PI3K/Akt	Human vascular endothelial cells	Dexamethasone

- Acute inhibitory effects (within 30 s) on basal $[Ca_{2+}]i$ in bronchial epithelial cells
- Comparable to triamcinolone, hydrocortisone,
- But not budesonide

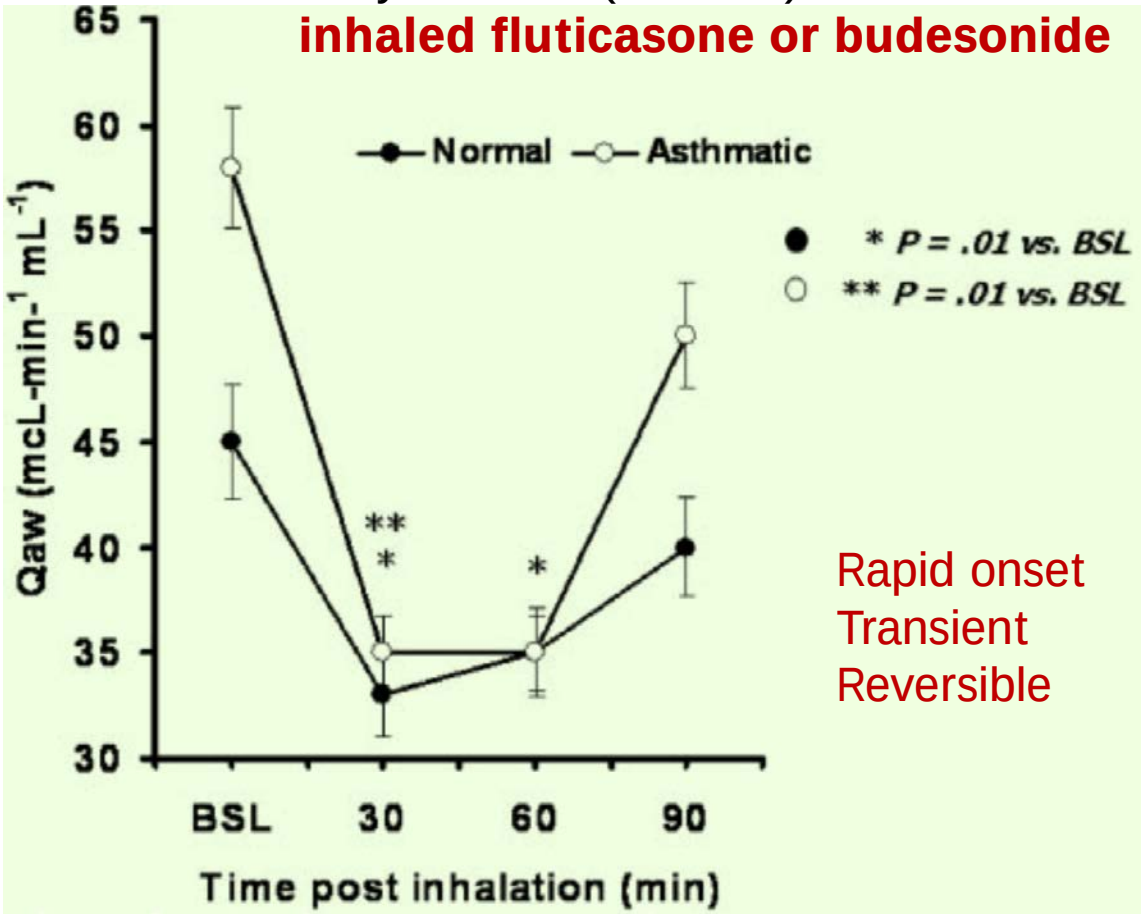
Trends in Pharmacological Sciences, January 2019, Vol. 40, No. 1

Membrane-initiated GCs signaling



혈관의 평활근 수축 생성, 혈류량 및 점막 부종 감소

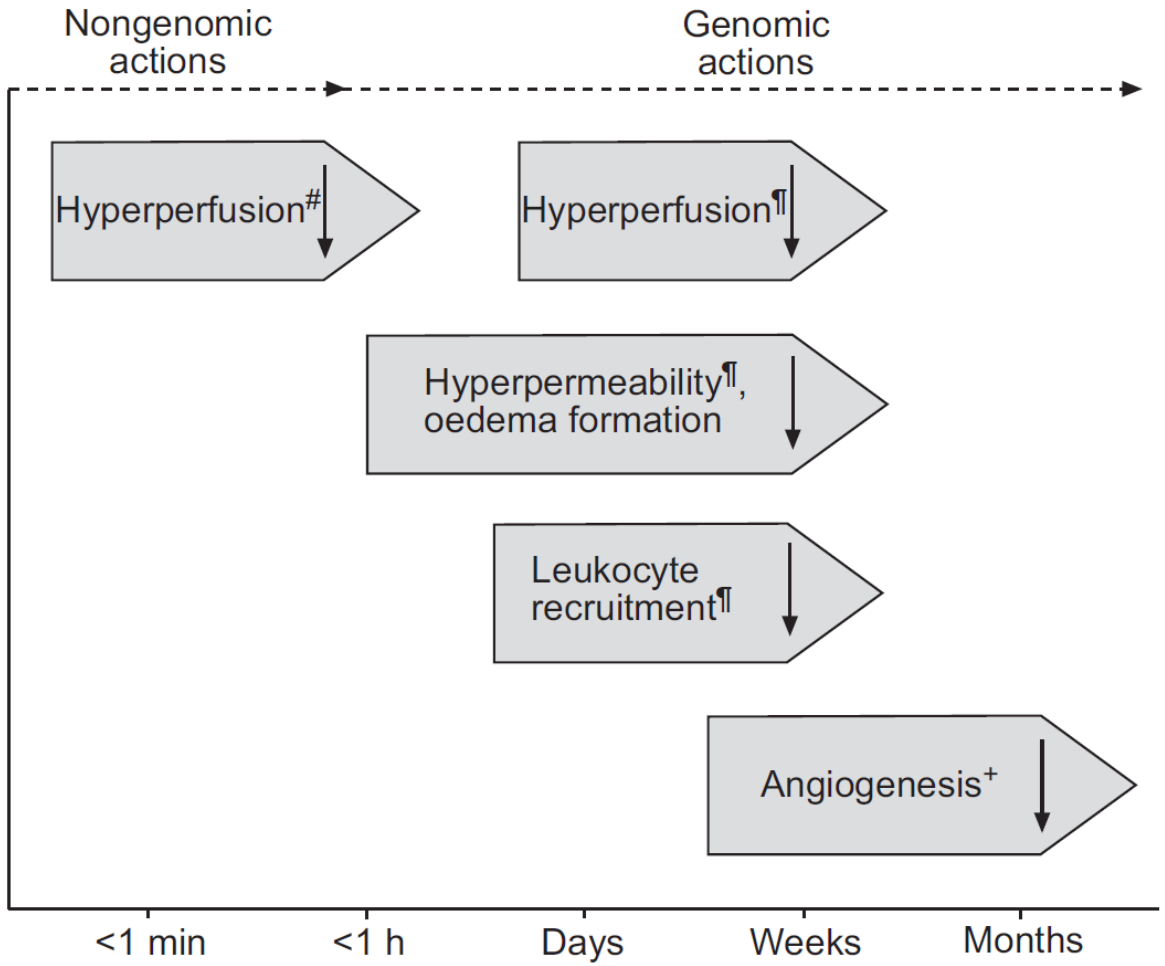
early benefits (1 to 2 h) the use of **inhaled fluticasone or budesonide**



Rapid onset
Transient
Reversible

Am J Respir Crit Care Med 2000;161:918–921

Inhaled corticosteroids: effects on the airway vasculature in bronchial asthma



- 스테로이드 전신 투여에서는 관찰되지 않음
- 국소 스테로이드는 항염증 효과 및 과관류를 줄이는 효과가 있다.
- ⇨ **응급 상황에서 전신 및 ICS 함께 사용하자**
- Budesonide, fluticasone > beclomethasone
- 30분 간격으로 3번 정도 ICS 사용

Eur Respir J 2006; 27: 172–187

Clinical Glucocorticoid (GC) Dosing and Cellular GC Actions

Genomic Actions (Receptor Saturation)	Unspecific Nongenomic Actions	Cytosolic Glucocorticoid Receptor (cGCR)–Mediated Nongenomic Actions
+ (<50%)	–	?
++ (>50% – <100%)	(+)	(+)
++(+) (almost 100%)	+	+
+++ ([almost] 100%)	++	+(+?)
+++ (100%)	+++	+(++?)

고용량 사용 시 실제 임상 효과의 주요 기전

From Buttgereit F, Straub RH, Wehling M, Burmester GR. Glucocorticoids in the treatment of rheumatic diseases. An update on mechanisms of action. Arthritis Rheum 2004;50:3408–17, with permission.)

Glucocorticoid Treatment Regimens: General Aspects

- **Low Dose**
  - Doses ~ 7.5 mg/day prednisone equivalent
  - Occupy less than 50% of the receptors
  - Used for maintenance or replacement therapy
  - 5단계 조절제를 제대로 사용함에도 불구하고
    증상 조절이 잘 되지 않거나, 악화가 잦은 경우
    저용량 경구스테로이드(≤7.5 mg/일 PDS)를
    추가 사용하면 **성인 중증 천식환자**에게 효과적인 경우가 있다.

    -GINA guideline 2023
  - Relatively few adverse effects

Glucocorticoid Treatment Regimens: General Aspects

- **Medium Dose** **0.5 mg/kg/day**
  - 7.5 mg ~ 30 mg/day PDS equivalent
  - Receptor saturation 50 ~100%
  - Effective in modulating disease activity
  - **만성 질환의 급성 악화(flare)**
    - **천식, 만성호산구폐렴, 두드러기, 알레르기 비염**
  - **약발진**-maculopapular rash, fixed eruption
  - Considerable and dose-dependent adverse effects

Systemic Glucocorticoid Therapy for Acute Exacerbations

- **천식**: PDS 30-50 mg/d, 3-7일간 사용
  - 질병조절제와 증상완화제를 2-3일간 증량하여도 호전이 없는 경우
  - PEF나 FEV1이 본인의 최고치에 비해 60% 미만으로 감소한 경우
  - 이전에 중증 급성 천식 악화가 있었던 경우

GINA guideline 2023

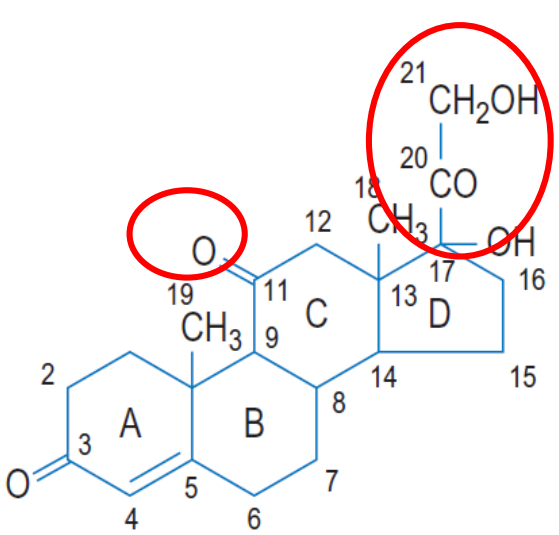
- **두드러기**: PDS 30~40 mg/d
  - 단기간 (10일 이내, 경우에 따라서는 1-3주)
  - 만성자발성두드러기의 치료로 스테로이드 사용을 권고하지 않는다

한국 만성두드러기 진료지침 2023

- **알레르기 비염**: PDS 0.5mg/kg/d, 5~7일
  - 비강 내 스테로이드제의 사용에도 조절되지 않는 알레르기 비염
  - 효과는 있다. (C , 권고를 고려할 수 있음)

2016 임상의를 위한 진료가이드라인 알레르기 비염
2022 임상의를 위한 진료지침 알레르기비염-언급 없음

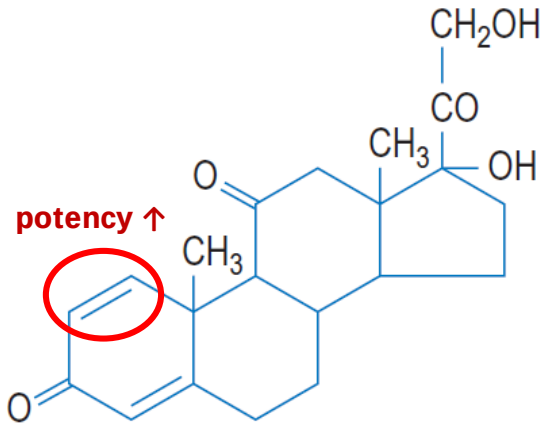
Molecular Structures of Cortisone and Commonly Used Glucocorticoids



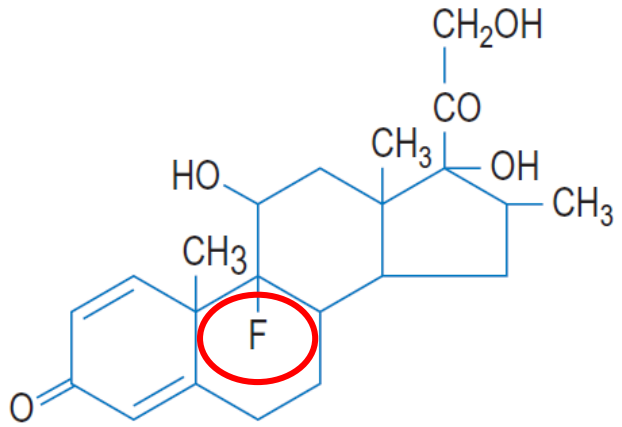
Cortisone

Binding affinity ↑

potency ↑

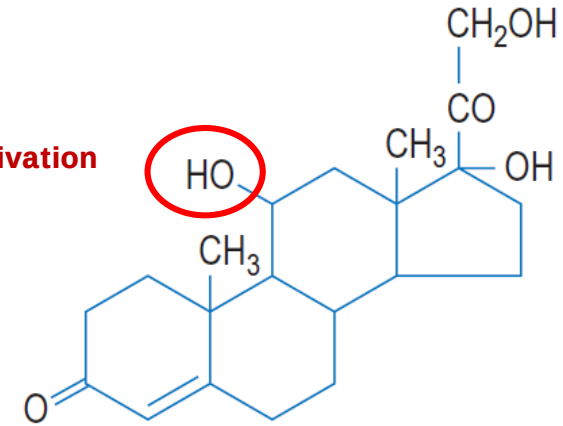


4 Prednisone

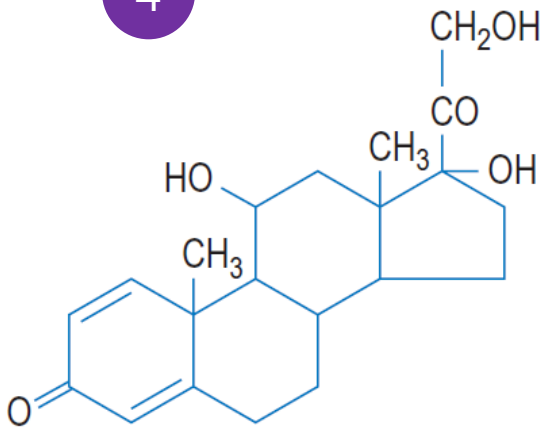


25 Dexamethasone

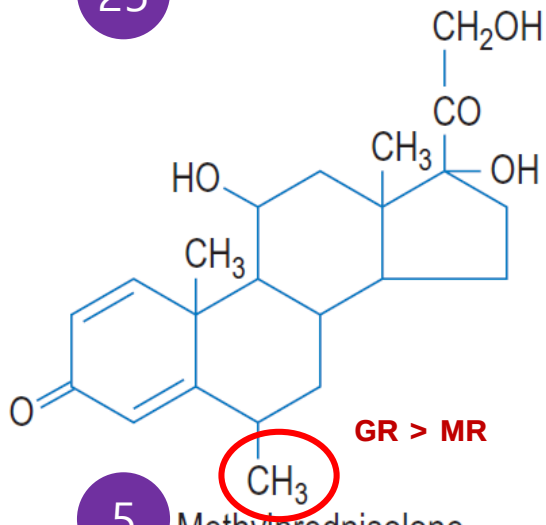
Activation



1 Hydrocortisone (cortisol)



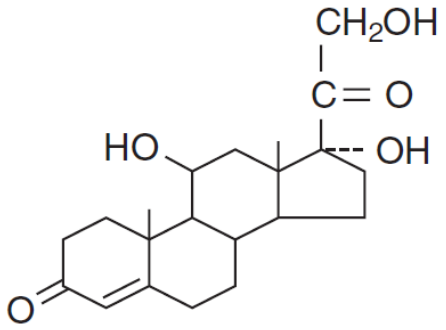
4 Prednisolone



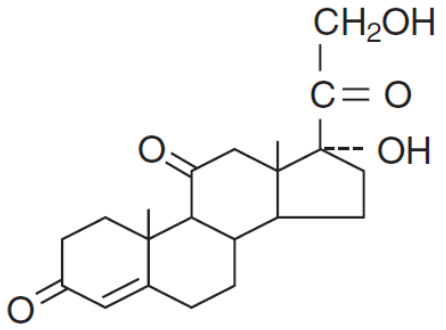
GR > MR

5 Methylprednisolone

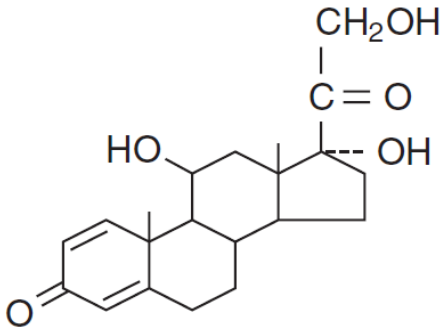
Structures of the natural glucocorticoid cortisol



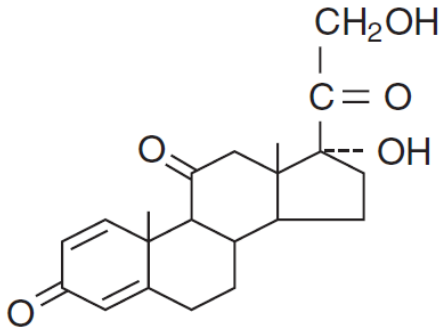
Cortisol



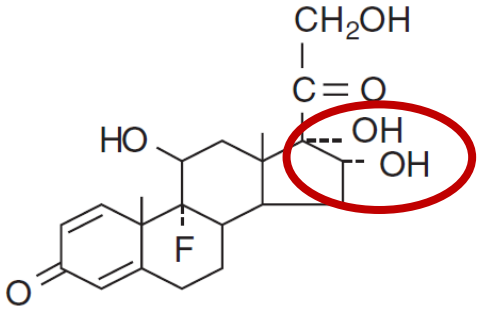
Cortisone



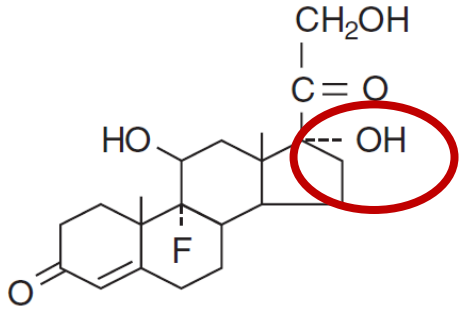
Prednisone



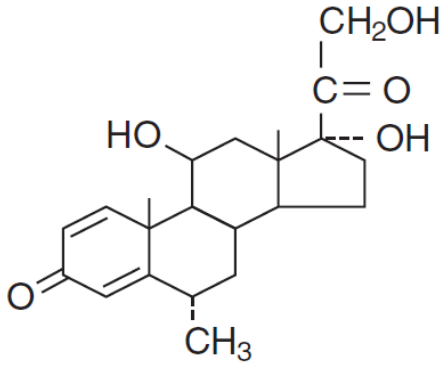
Prednisone



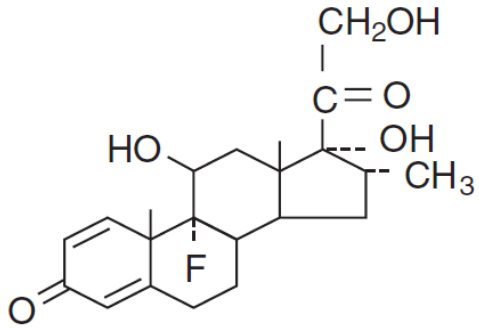
Triamcinolone



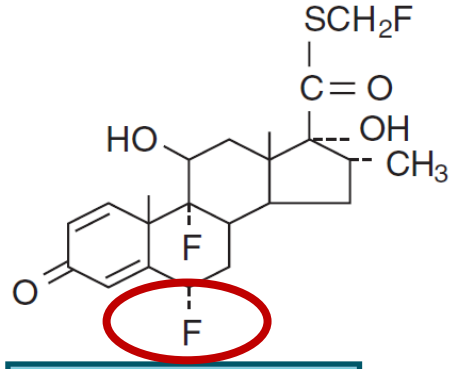
Fludrocortisone



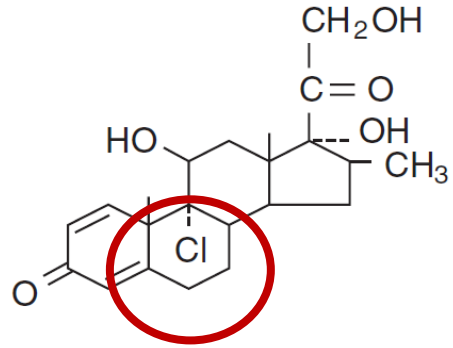
Methylprednisolone



Dexamethasone



Fluticasone



Beclomethasone

Relative potencies of common glucocorticoids

Equivalent dosages (relative potencies) to produce classic genomic effects

Drugs	Potency	Equivalent dose*	Anti-inflammatory activity	Na+ retention	Duration of Action (hr)†	Plasma Half-life(hr)
Oral drugs						
Hydrocortisone	1	20 mg	1	1	8~12	1.2
Cortisone	0.8	25 mg		0.8	8~12	1.2
Prednisolone	4	5 mg	3	0.8	12~36	2.5
Prednisone	4	5 mg	3	0.8	12~36	3.3
Methylprednisolone	5	4 mg	6.2	0.5	12~36	2.8
Triamcinolone	5	4 mg	5	<0.01	12~36	-
Dexamethasone	25	0.75 mg	30~40	<0.01	36~72	3.5
Betamethasone	25	0.75 mg	Less effect systemically	<0.01	36~72	3.3
Inhaled drugs						
Budesonide	3750	400 μg			1.5~2.8	
Fluticasone	7200	200 μg			3.1~14	
Momentasone	8800	200/400 μg			4.5	
des-Ciclesonide	4800	320 μg			0.7~7	
Beclomethasone;BDP	2100	400 μg			0.5	

Very low nongenomic potency

nonspecific nongenomic effect of methylPDS(3) > PDS(1)

*Equivalent to hydrocortisone for oral drug(mg) and to BDP for inhaled drug(μg)

only valid for doses less than 100 mg prednisone equivalent

†Biologic half-life(hours)

Systemic Glucocorticoid Therapy for Acute Exacerbations

- IV GCs; hydrocortisone, betamethasone, methylprednisolone, and **dexamethasone**
- **MethylPDS**; drug of choice for therapy
  - 항염증 효과 크다(nongenomic effect),
  - 미네랄글루코코르티코이드 효과가 적다,
  - Hydrocortisone에 비하여 가격 저렴
  - 하루 한 번 투여 가능 (반감기)

PDS 5 mg/T; 15원

methylPDS 4 mg/T; 98원

주사용
methylPDS 40mg; 1407원

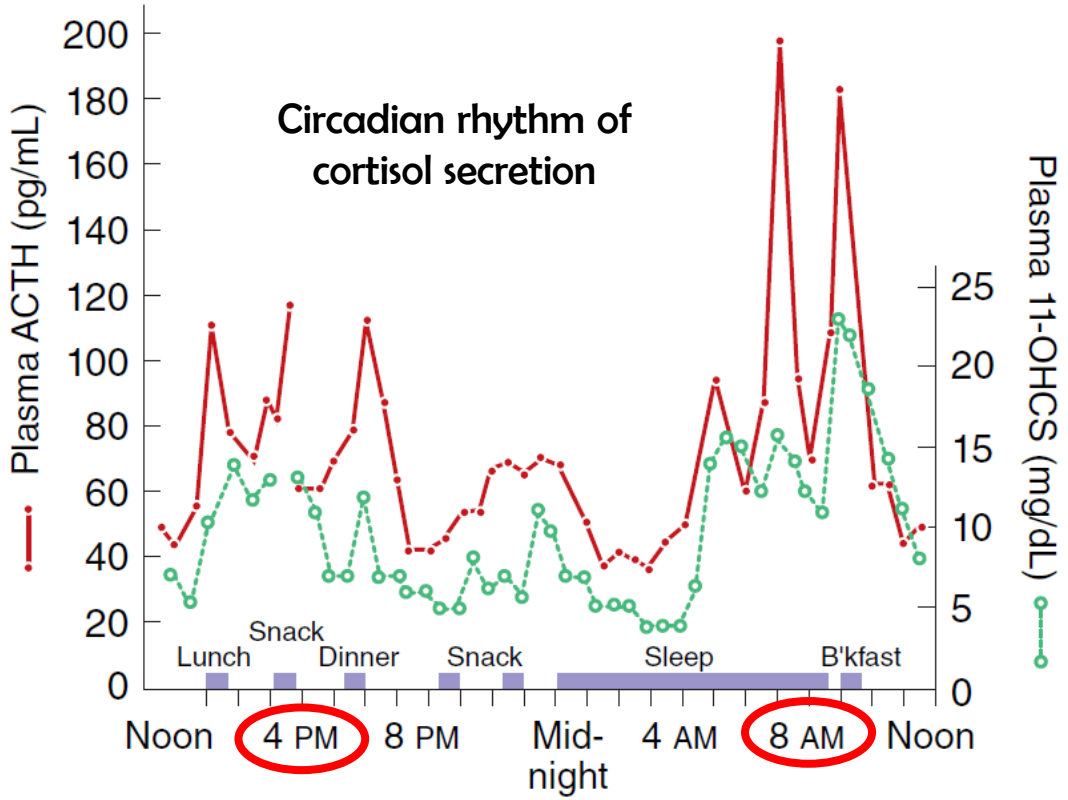
- Typical short course of **oral** therapy
  - 경구 vs 주사 – 효능이나 작용 시작시간 차이 미비
  - 주사 부위 근육에 대한 부작용이 적다.
  - 용량을 필요한 만큼 최소량으로 조정하기가 수월하다
  - 치료 비용 절감

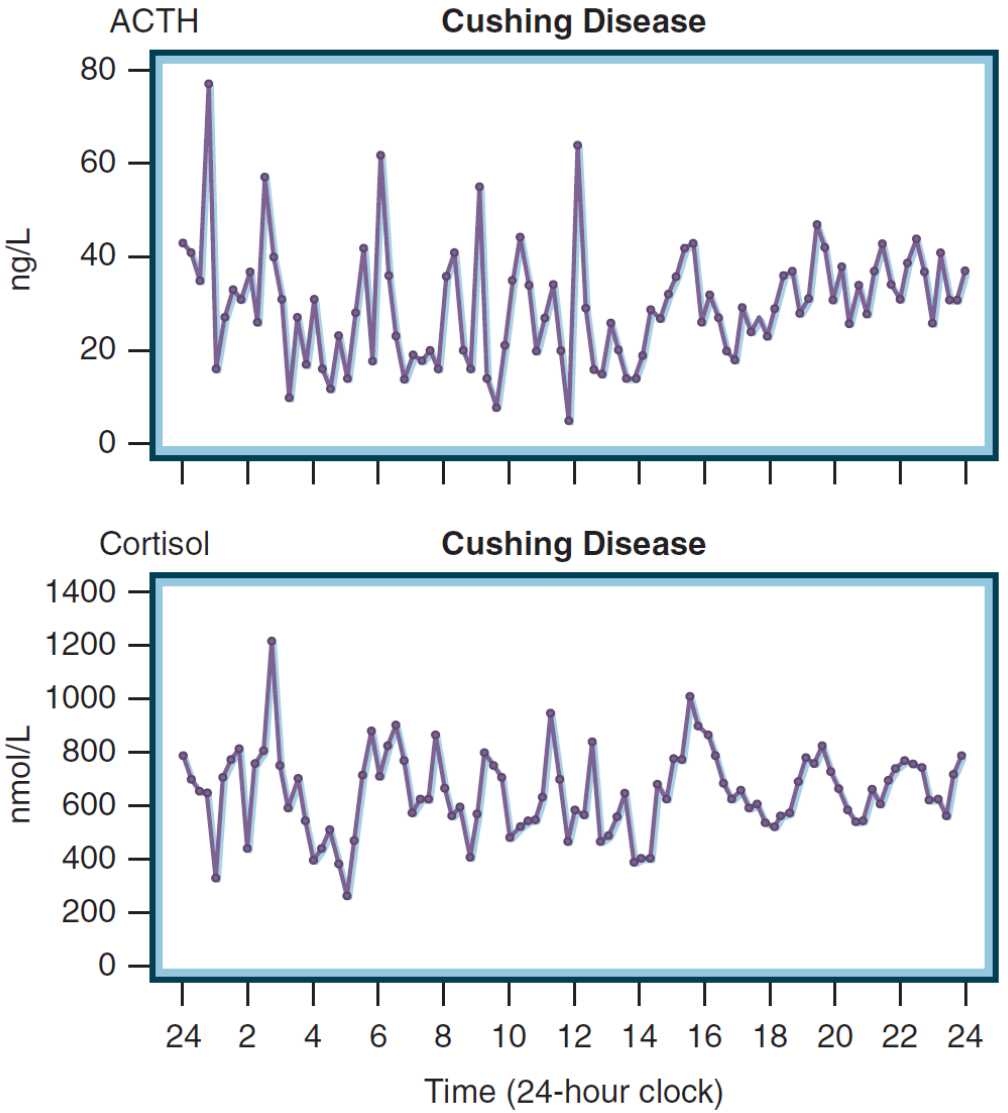
Glucocorticoid Treatment Regimens: General Aspects

- **High Dose** **1.0 mg/kg/day**
  - 30 mg ~ 100 mg/day of PDS equivalent
  - 100mg PDS – almost complete saturation(genomic effect full)
  - **Nongenomic effects**-additional therapeutic benefit
  - Initial treatment for **subacute diseases**
  - Acute form eosinophil-related disease
    - **Hypereosinophilic syndrome, Acute eosinophilic pneumonia, EGPA**
  - Drug eruption
    - **DRESS syndrome, SJS**
  - **Anaphylaxis**
  - Cannot be administered over the long term

Systemic Glucocorticoid Therapy for Acute Exacerbations

- Daily endogenous secretion of cortisol is about 10 to 20 mg
- Low to medium dose – 1일 1회
  High dose – 필요 시 2회 분복 (2:1 비율)





Glucocorticoid Treatment Regimens: General Aspects

- 14일 이내 사용 기간이라면 tapering은 꼭 필요하지는 않다.
  - Requiring prolonged treatment for more severe or refractory exacerbations,
  - CEP, drug eruption, idiopathic anaphylaxis
  - 매 1-2주 마다 5-10 mg씩 감량, 또는 30% every 4-days
- **Alternate-Day Regimens**
  - Aim of minimizing undesirable adverse effects (suppression of HPA axis)
  - Single dose : 격일제(홀수날) 아침
    하루 유지 용량의 2배량 투여
  - Often experience breakthrough symptoms on the second day

Glucocorticoid Treatment Regimens: General Aspects

- **Very High Dose** **2.0 mg/kg/day**
  - Above 100 mg of prednisone equivalent per day
  - Virtually 100% cGCR, affect the pharmacodynamics (*e.g.,* receptor off-loading and reoccupancy), receptor synthesis and expression
  - **Nongenomic effects**-additional therapeutic benefit
  - Initial treatment for acute or life-threatening exacerbations

Glucocorticoid Treatment Regimens: General Aspects

- **Pulse Therapy**
  - ≥ 250 mg/day prednisone equivalent(usually intravenously) for a short period (typically 1–5 days, rarely longer)
  - Immediate effect of nongenomic potencies
  - Make a crucial contribution to the therapeutic effect by terminating acute exacerbations(particularly severe forms of rheumatic diseases, such as SLE, vasculitis, polymyositis, and RA)

Take home message

- Genomic(slow) vs nongenomic(rapid) reaction
- Nongenomic effects of GCs는 스트레스 상황에서 유용하다
- 알레르기 질환에서 전신 스테로이드 사용 시
  - 무기질코르티코이드 효과가 적은 것
  - 질환 요구도에 따른 충분한 용량(0.5 ~1.0 mg/kg/day)
  - 아침에 단일 경구 복용 (효과 & 부작용)
  - 장기간 필요 시 격일제 요법