

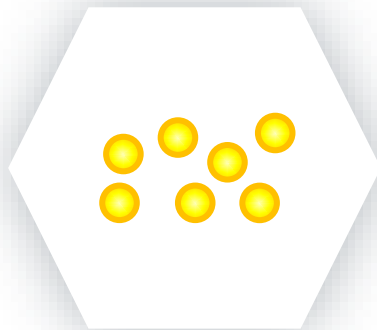
# Understanding Cortisol– Glucocorticoid Receptor Signaling

---

# Cortisol activity is influenced by cortisol levels and GR sensitivity

## Cortisol levels<sup>1,2</sup>

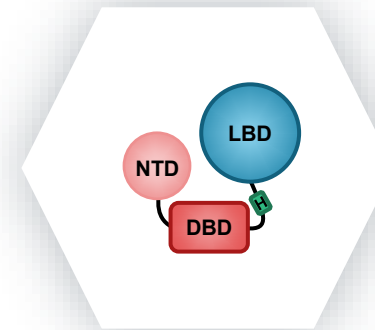
- **Cortisol synthesis**
- **Serum cortisol levels**
  - **CBG affinity and concentrations**
- **11 $\beta$ -HSD 1/2 regulation**



Cortisol

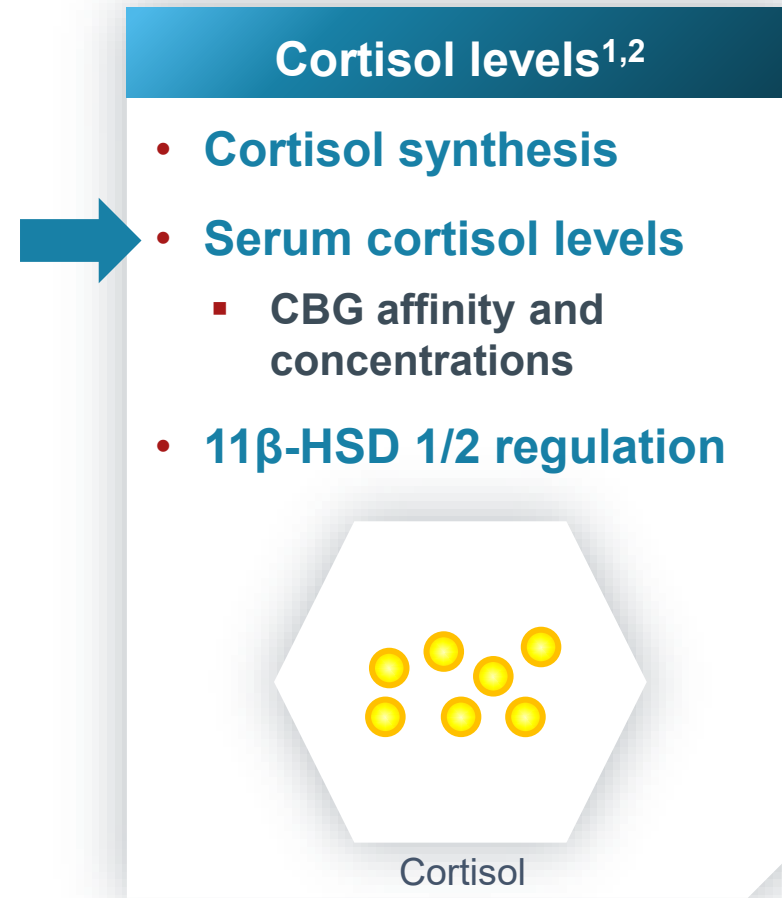
## GR sensitivity<sup>1,2</sup>

- **GR mutations**
- **GR isoforms/variants**
- **GR post-translational modifications**



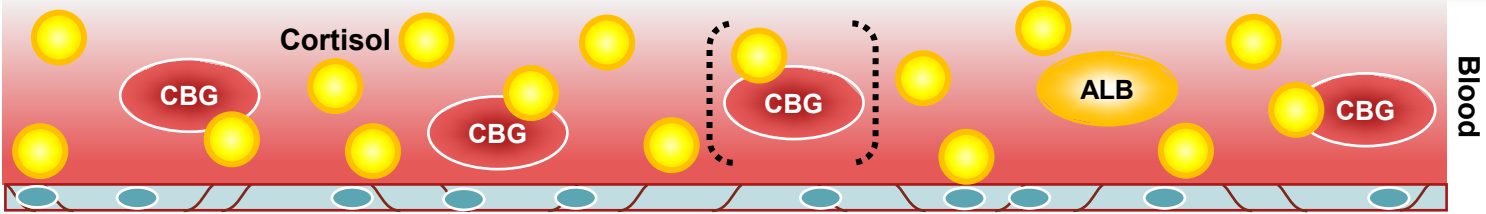
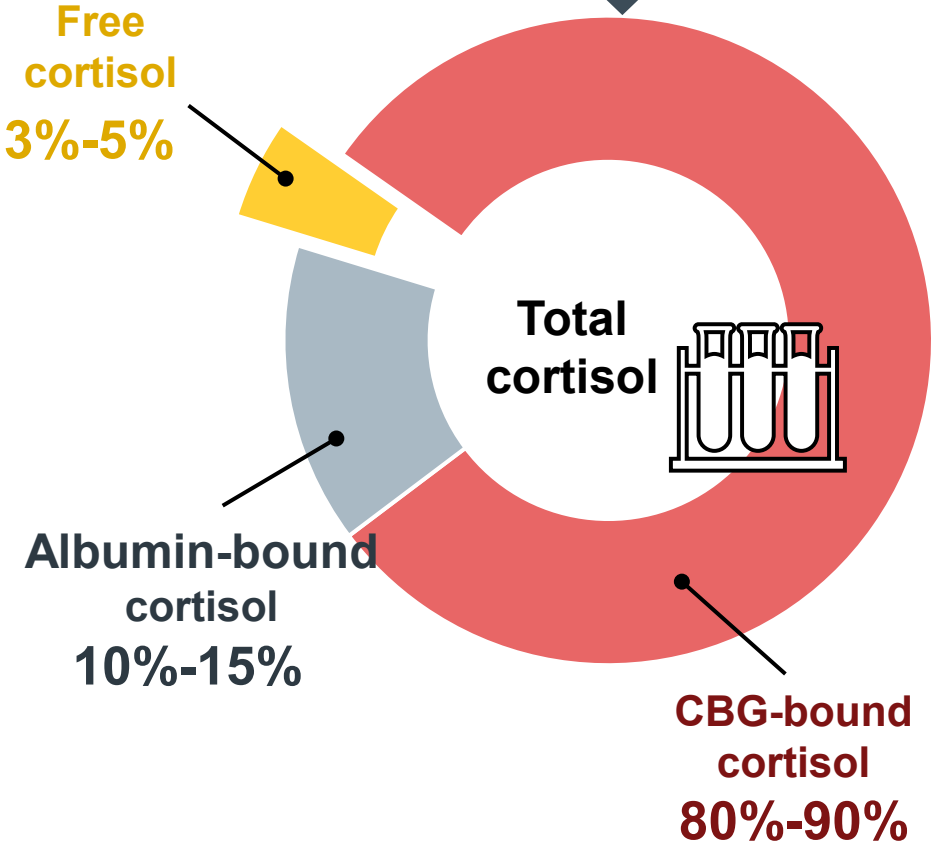
GR

# Cortisol activity is influenced by cortisol levels



# Cortisol is kept inactivated in the plasma via binding to CBG

Distribution of cortisol in human blood<sup>1,2</sup>



Several factors can alter CBG levels, and therefore total cortisol levels, thereby interfering with test results<sup>3,4</sup>

Factor	CBG levels	Cortisol levels	
<ul style="list-style-type: none"> <li>• Pregnancy</li> <li>• Oral contraceptive<sup>a</sup></li> <li>• Mitotane<sup>a</sup></li> </ul>	↑	↑	<b>Increased false-positive results</b>
<ul style="list-style-type: none"> <li>• Nephrotic syndrome</li> <li>• Malnutrition</li> <li>• Hypothyroidism</li> </ul>	↓	↓	<b>Increased false-negative results</b>

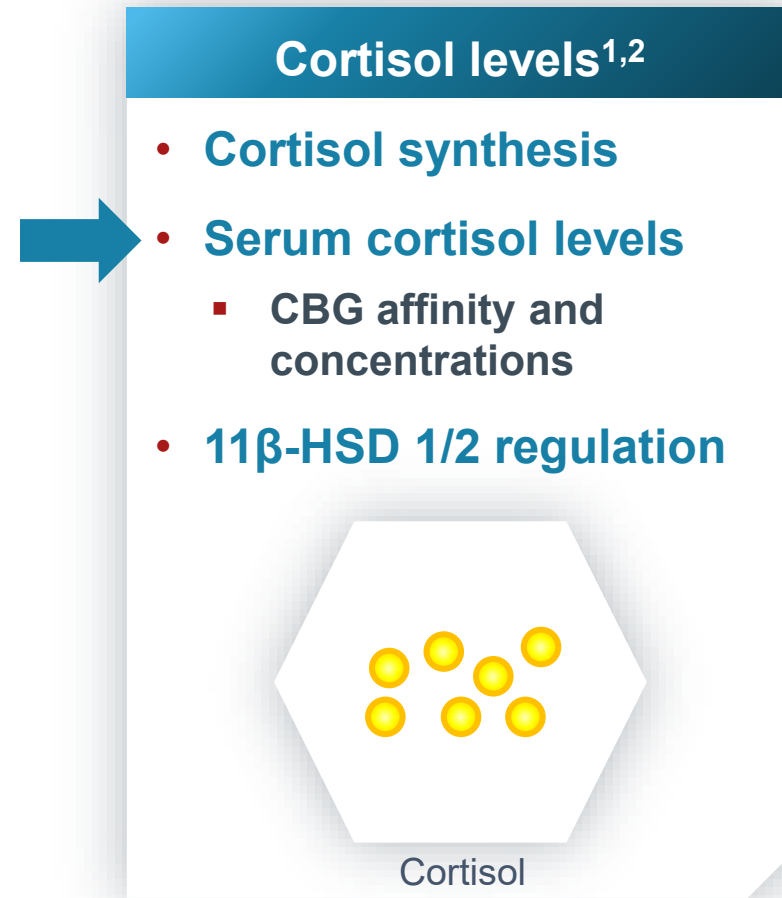
ALB=albumin.

<sup>a</sup>Should be discontinued for at least 6 weeks prior to testing.

1. Choi MH. *Endocrinol Metab (Seoul)*. 2022;37(4):599-607. 2. Timmermans S, et al. *Front Immunol*. 2019;10:1545. doi:10.3389/fimmu.2019.01545

3. Nenke MA, et al. *J Endocr Soc*. 2017;1(3):202-210. 4. Farinelli DG, et al. *Endocr Pract*. 2023;29(12):986-993.

# Cortisol activity is influenced by cortisol levels



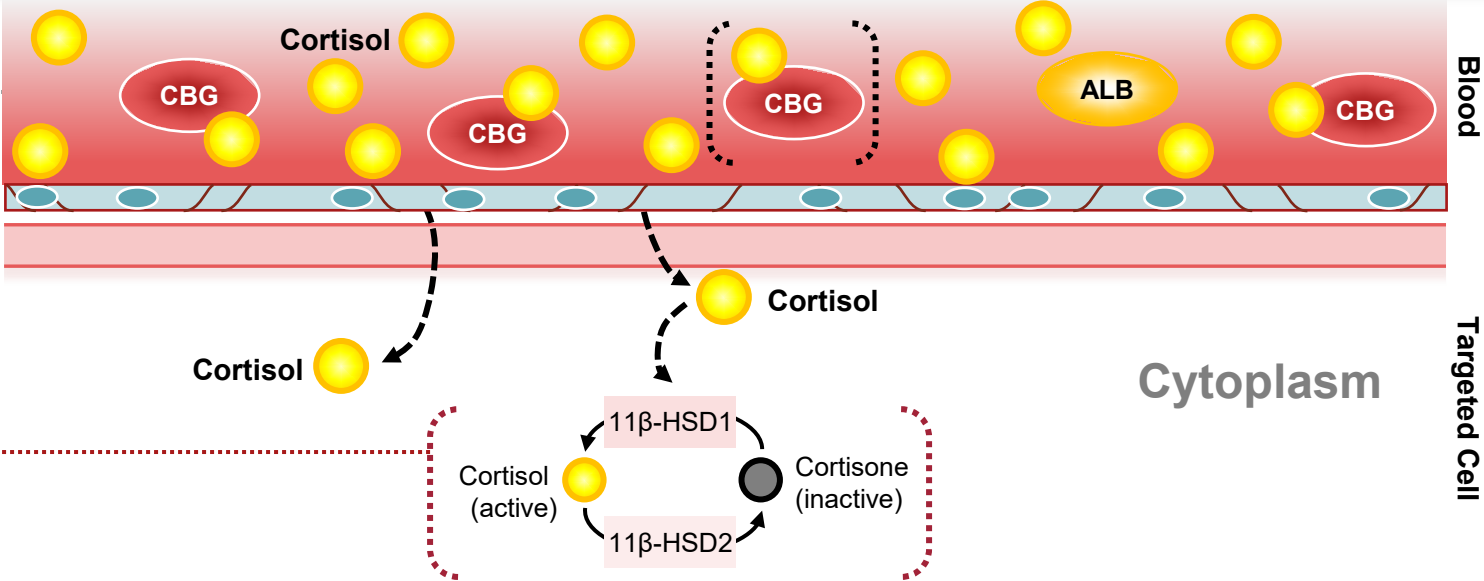
# Cortisol activity is highly regulated<sup>1,2</sup>

## Bloodstream

Cortisol is kept inactive in the plasma via binding to **corticosteroid-binding globulin (CBG)**

## Cytoplasm

Activation and deactivation of cortisol is regulated by the **11 $\beta$ -HSD1/2** enzymes



# Cortisol activity is highly regulated (cont.)<sup>1,2</sup>

## Bloodstream

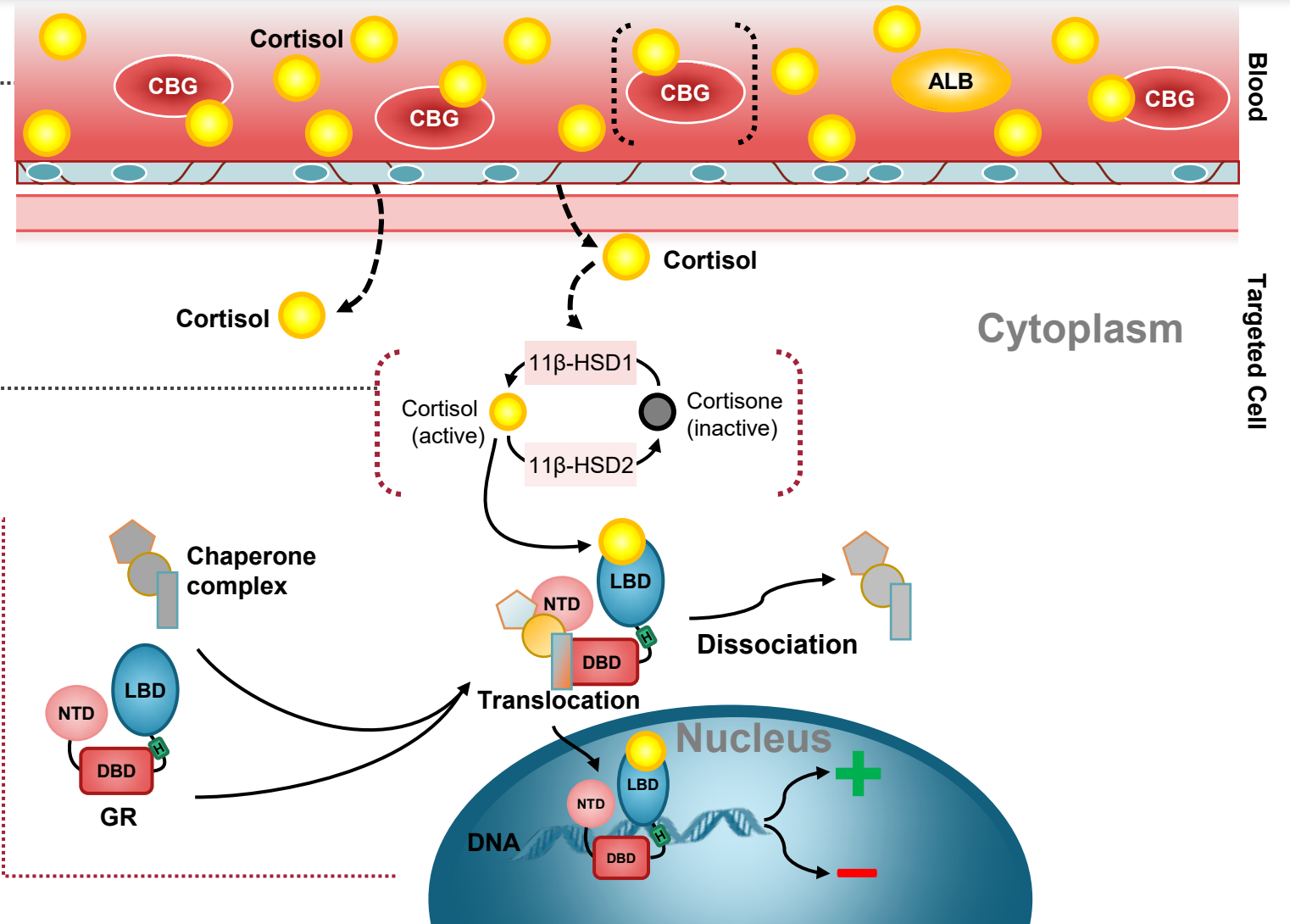
Cortisol is kept inactive in the plasma via binding to **corticosteroid-binding globulin (CBG)**

## Cytoplasm

Activation and deactivation of cortisol is regulated by the **11 $\beta$ -HSD1/2** enzymes

## Cortisol-GR complex binding to DNA

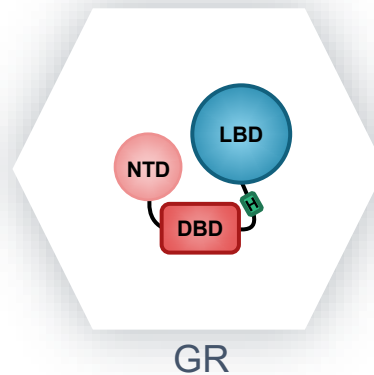
It can mediate the **upregulation** (transactivation) or **downregulation** (transrepression) of numerous genes



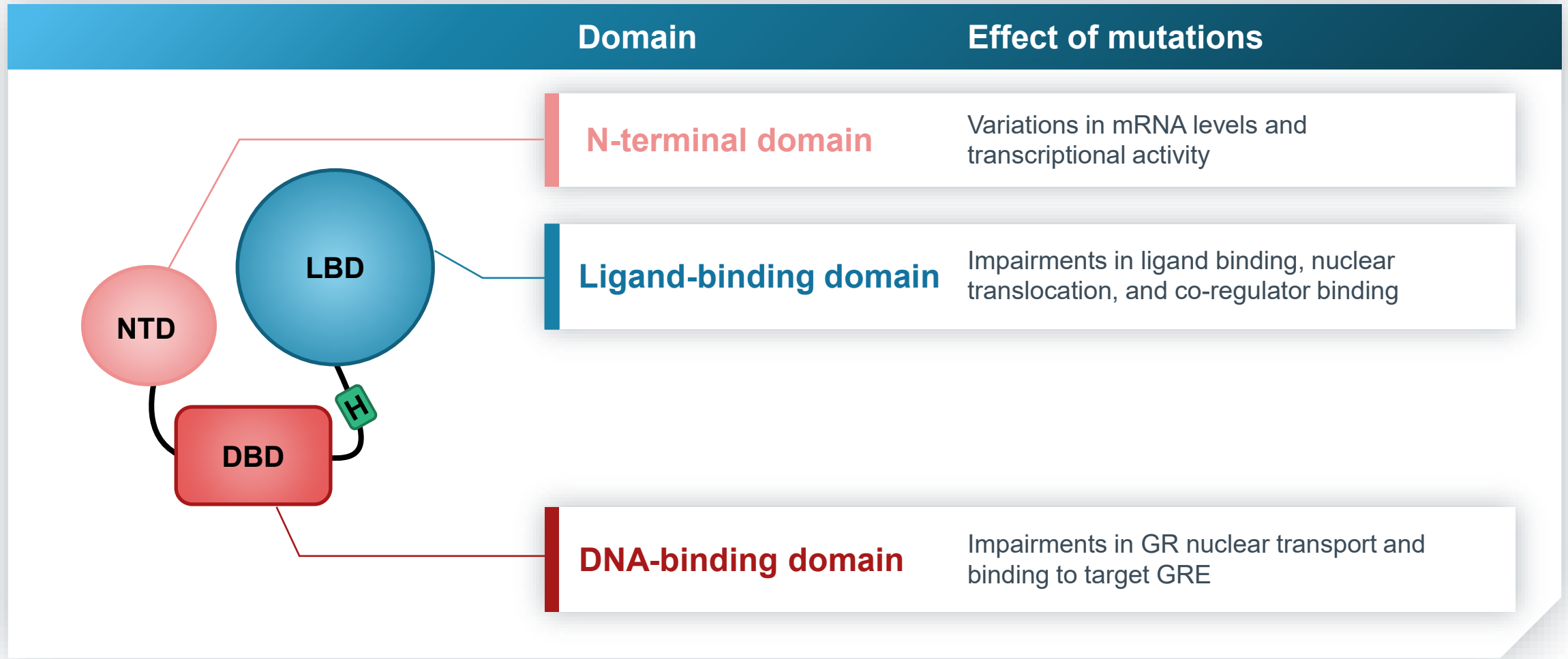
# Cortisol activity is influenced by GR sensitivity<sup>1,2</sup>

## GR sensitivity<sup>1,2</sup>

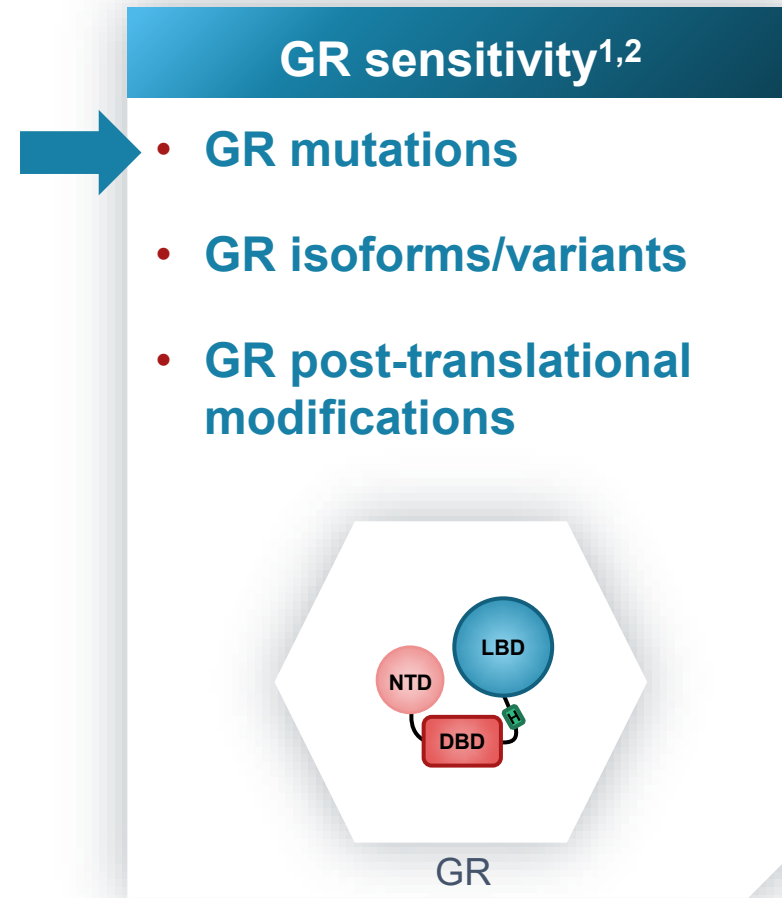
- GR mutations
- GR isoforms/variants
- GR post-translational modifications



# Mutations in the GR gene can alter receptor function and sensitivity to cortisol

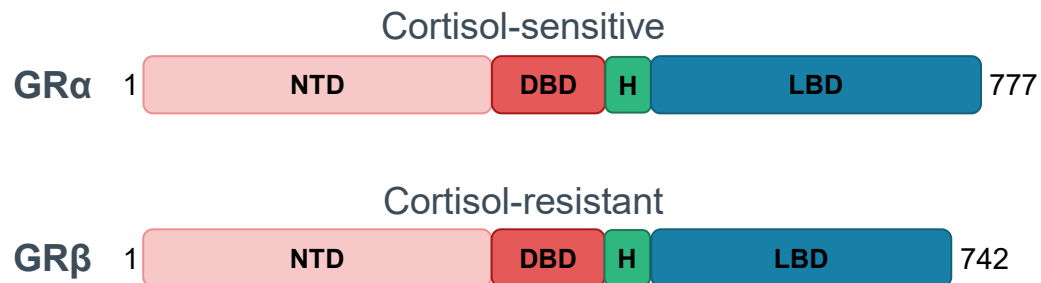


# Cortisol activity is influenced by GR sensitivity<sup>1,2</sup>



# Tissue- and cell-specific distribution of GR variants influences cortisol-GR signaling

## GR isoforms<sup>1,2</sup>

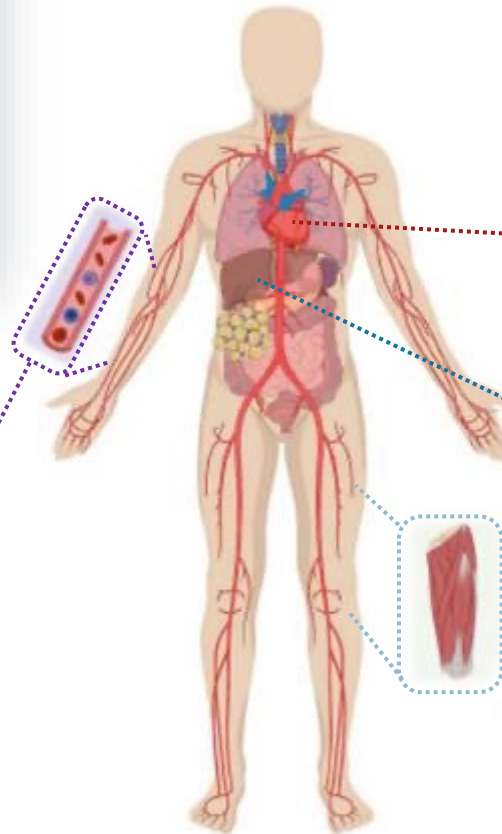


### Immune System

**Thymus:** High GRβ expression, GRα >7-8x GRβ, and GRα-B >GRα-A

**Dendritic cells:** High GRα-D

## Distribution of GR isoforms/variants<sup>3-7</sup>



### Cardiovascular System

**Heart:** GRα >15x GRβ

### Liver and Adipose

**Pancreas:** High GRα-C

**Liver:** GRα >20-30x GRβ

**Adipose:** GRα >20x GRβ

### Muscle

**Skeletal muscle:** Low GRα and GRβ; GRα >40x GRβ

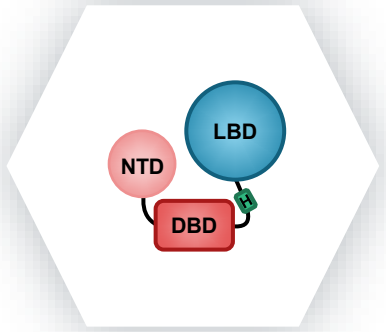
1. Timmermans S, et al. *Front Immunol.* 2019;10:1545. doi:10.3389/fimmu.2019.01545 2. Lu NZ, Cidlowski JA. *Trends Cell Biol.* 2006;16(6):301-307. 3. DuBois DC, et al. *Steroids.* 2013;78:312-320. 4. Lu NZ, Cidlowski JA. *Ann NY Acad Sci.* 2004;1024:102-123. 5. Lu NZ, Cidlowski JA. *Mol Cell.* 2005;18:331-342. 6. Sinclair D, et al. *Mol Psych.* 2011;16:504-515. 7. Vandevyver S, et al. *Endocr Rev.* 2014;35:671-693.

# Cortisol activity is influenced by GR sensitivity<sup>1,2</sup>



**GR sensitivity<sup>1,2</sup>**

- GR mutations
- GR isoforms/variants
- GR post-translational modifications



GR

The diagram illustrates the structure of the Glucocorticoid Receptor (GR). It is shown as a white hexagon containing three colored circles: a red circle labeled 'NTD' (N-terminal domain), a blue circle labeled 'LBD' (ligand-binding domain), and a red rectangle labeled 'DBD' (DNA-binding domain). The NTD and LBD are connected to the DBD by thin lines, and the LBD is also connected to a small green square. The entire structure is labeled 'GR' below it.

# Post-translational modifications of the GR protein can modulate the functionality of GR

## Post-translational modifications of GR

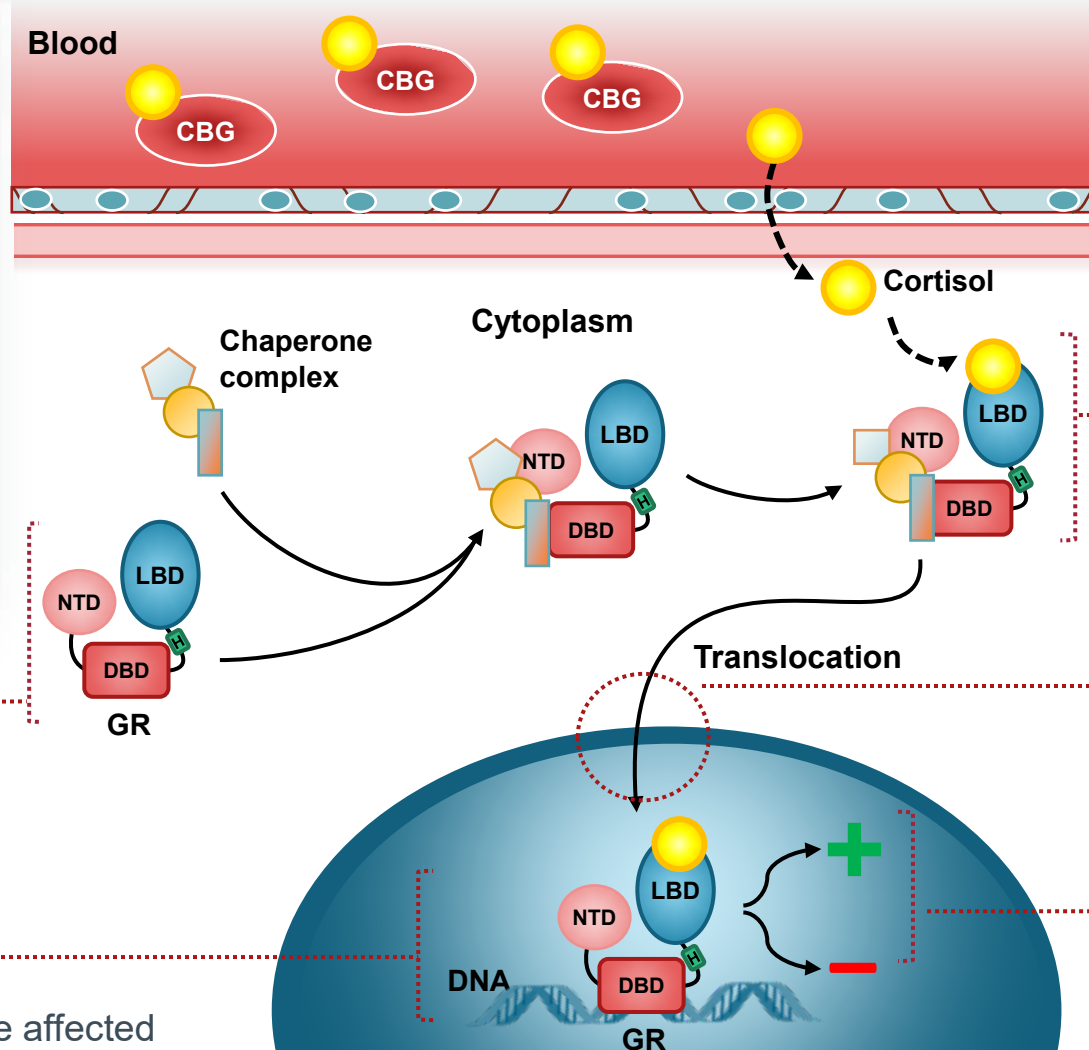
- Phosphorylation
- Ubiquitination
- SUMOylation
- Acetylation
- Nitrosylation
- Oxidation

### Protein stability

Receptor can be degraded, or its expression can be upregulated

### DNA binding

Binding affinity and location can be affected



### Ligand binding

Changes to binding affinity

### Protein transport

Modifications in the ability to translocate into the nucleus

### Transcriptional activity

Changes in activity/effect

