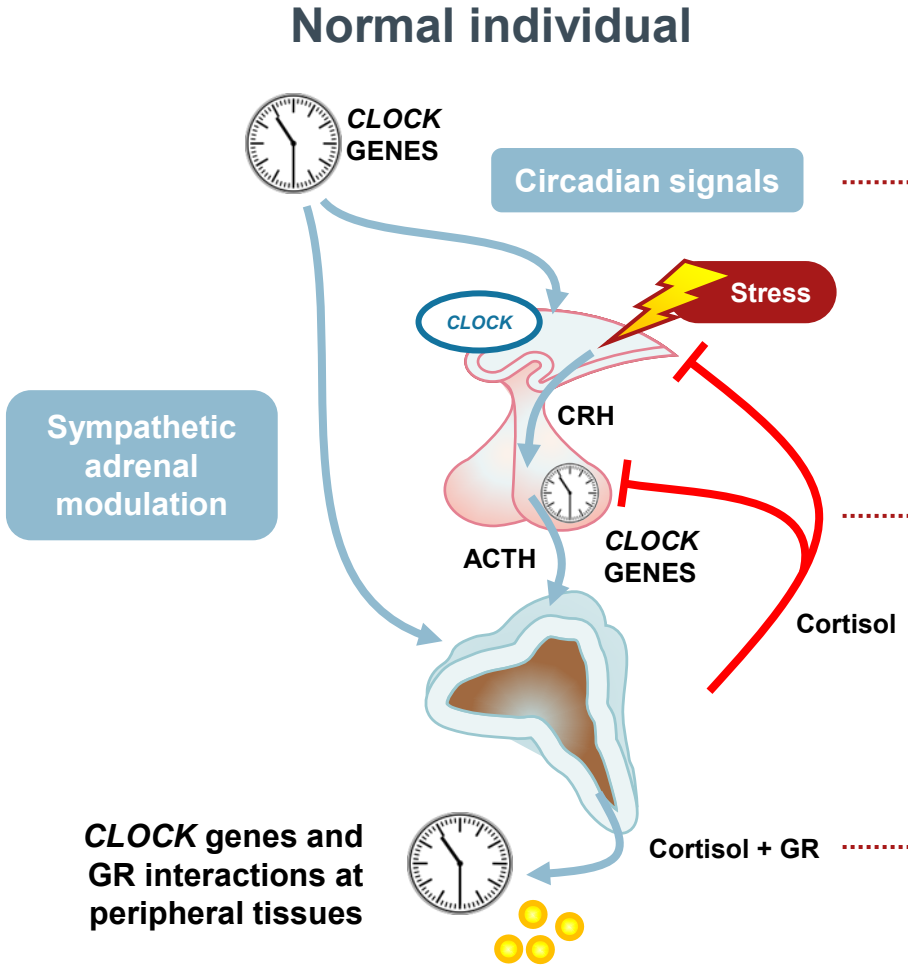
What Causes Hypercortisolism?

Cortisol production: Circadian signaling

Normal cortisol circadian rhythm follows a diurnal variation

06h 10h 14h 18h 22h 02h 06h



Circadian timing signals are propagated downstream from the hypothalamic suprachiasmatic nucleus *CLOCK* genes to the HPA axis

Cortisol can influence *CLOCK* genes via the feedback loop at the HPA axis, which oscillates at a periodicity of ~24 hours

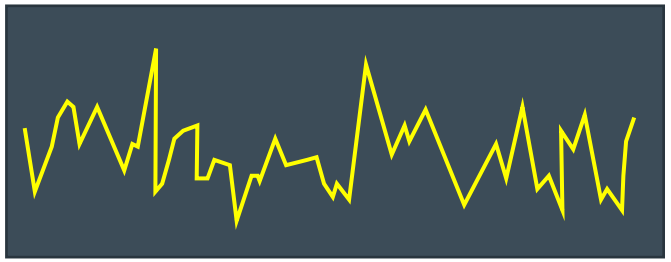
Crosstalk between *CLOCK* genes and GRs helps modulate the effects of cortisol circadian rhythm in the peripheral tissues

ACTH=adrenocorticotropic hormone; CRH=corticotropin-releasing hormone; GR=glucocorticoid receptor; HPA=hypothalamic-pituitary-adrenal.

Moreira AC, et al. *Eur J Endocrinol*. 2018;179:R1-R18.

Excess cortisol can impair the circadian rhythm

Loss of cortisol circadian rhythm in hypercortisolism



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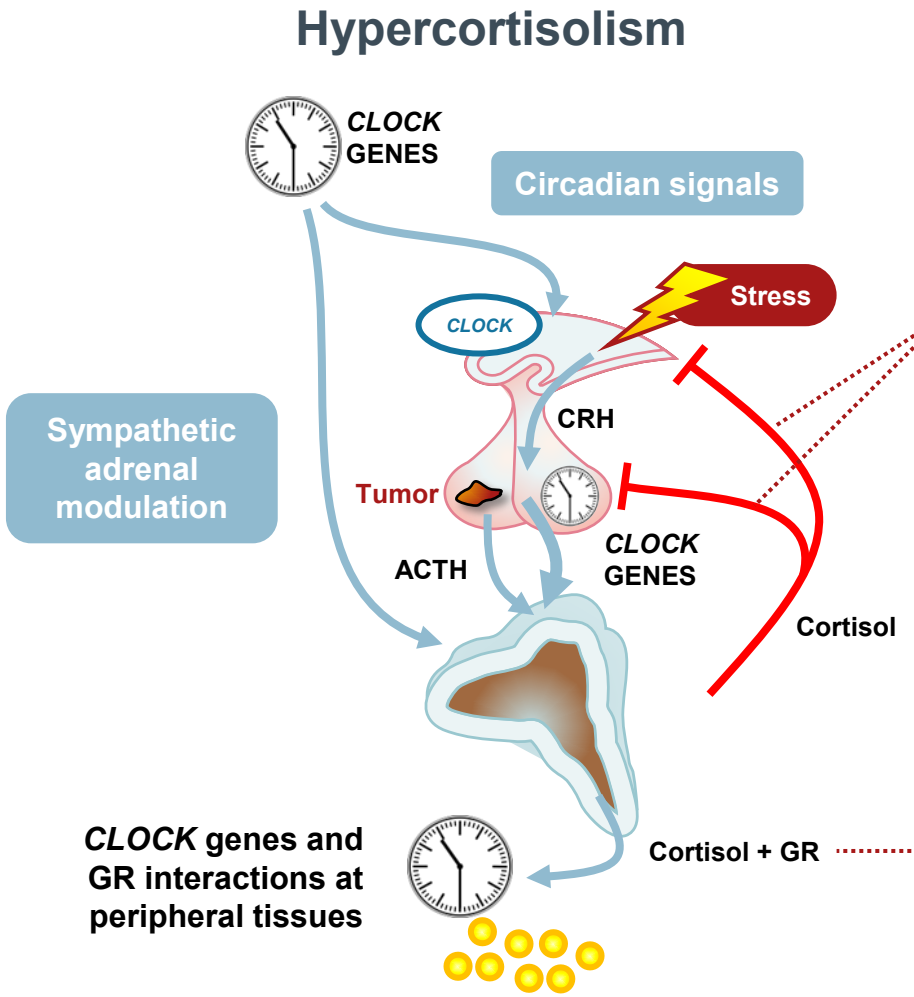


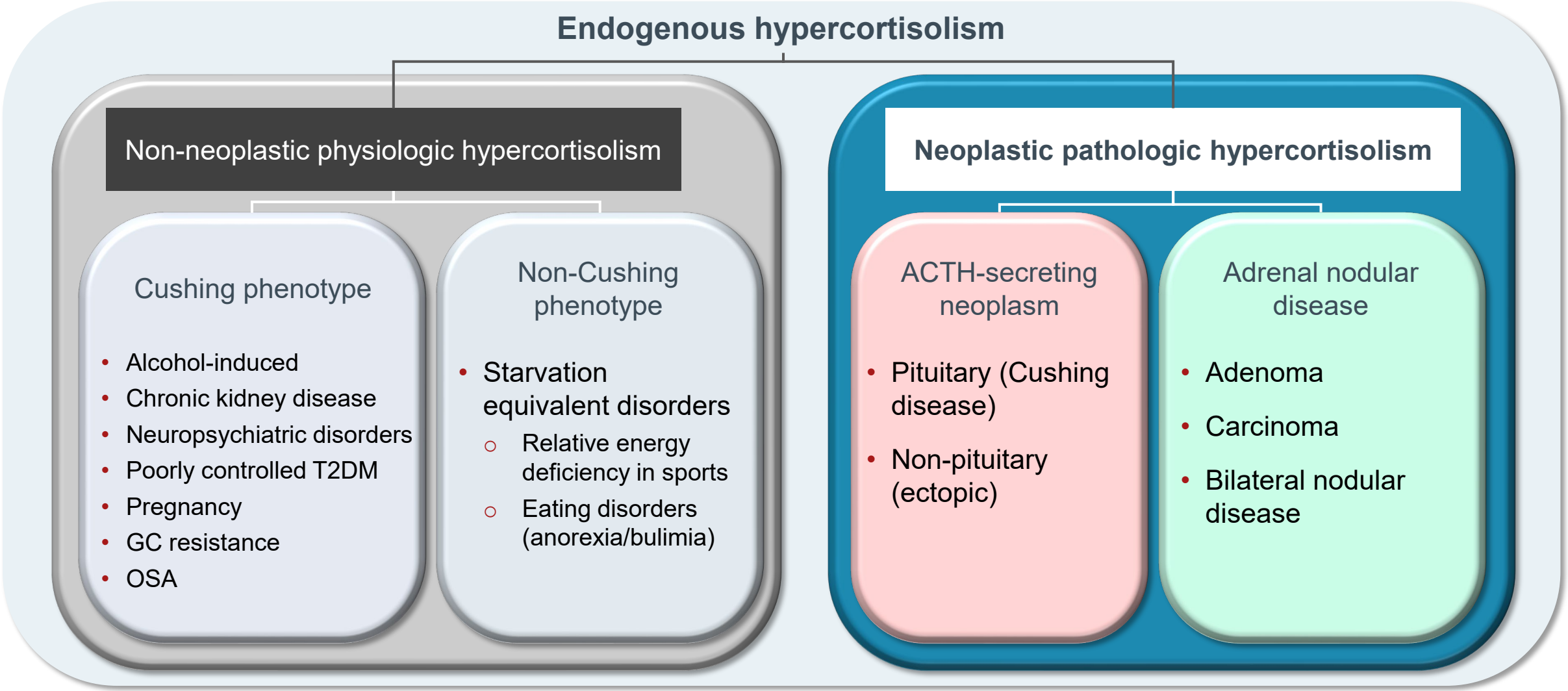
Increased cortisol impairs circadian CRH release and potentially also the HPA *CLOCK* genes, leading to **abnormal cortisol rhythm.**

Adenomas may also be resistant to the cortisol feedback loop, resulting in **loss of pulsatile ACTH signaling.**[1,2]

CLOCK system dysregulation in target tissues leads to intermediary metabolic dysregulation and clinical features of Cushing's syndrome.[1]

1. Moreira AC, et al. *Eur J Endocrinol*. 2018;179:R1-R18; 2. Lim CT, et al. In: *Endotext [Internet]*. South Dartmouth (MA): MDText.com, Inc.; 2000-2020 Nov 7.

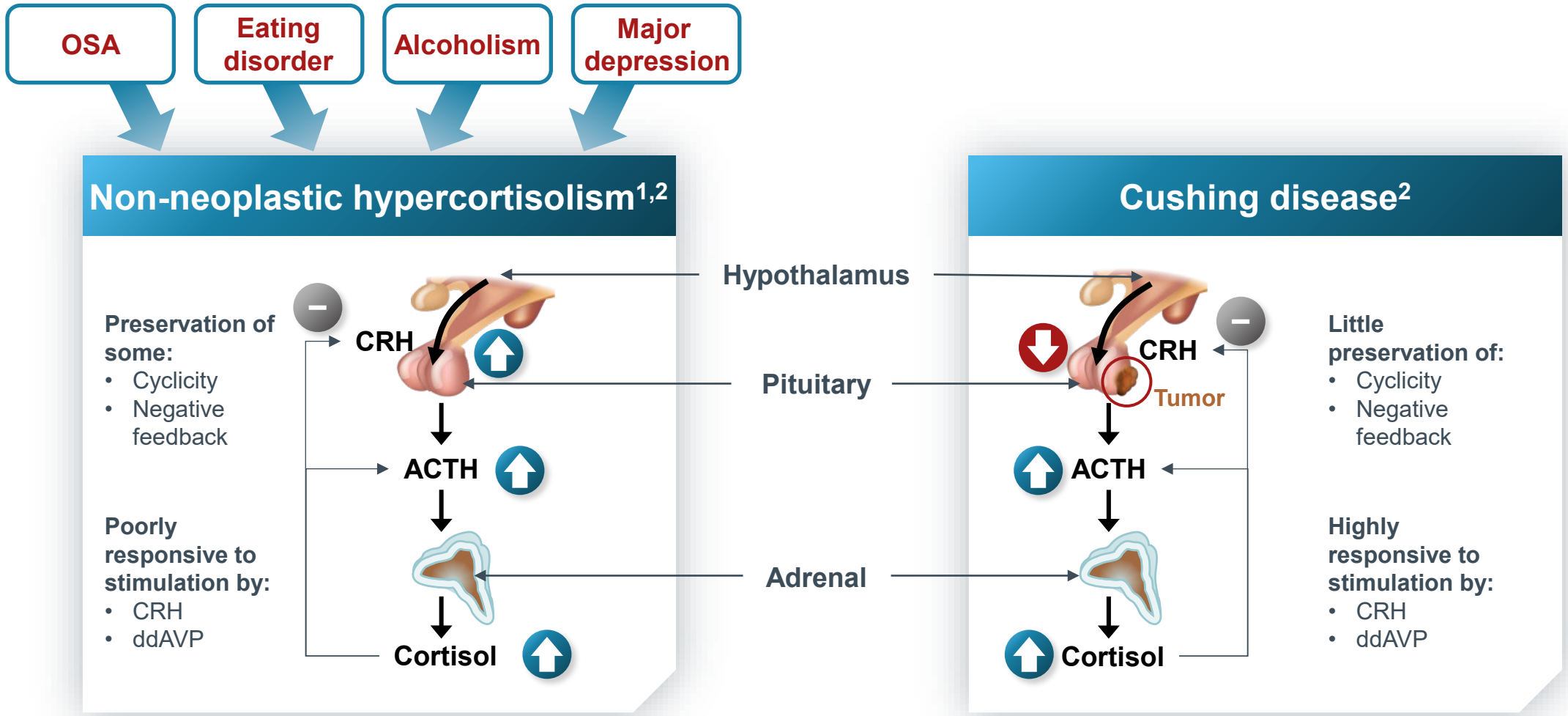
Different etiologies of endogenous hypercortisolism



GC=glucocorticoid; OSA=obstructive sleep apnea; T2DM=type 2 diabetes mellitus.

Findling JW, Raff H. *J Endocr Soc.* 2023;7(8):bvad087. doi:10.1210/jendso/bvad087

Salient features of non-neoplastic hypercortisolism



ddAVP=1-deamino-8-D-arginine vasopressin (desmopressin).

1. Findling JW, Raff H. *J Endocr Soc*. 2023;7(8):bvad087. doi: 10.1210/jendso/bvad087 2. Chabre O. *Ann Endocrinol (Paris)*. 2018;79(3):138-145.