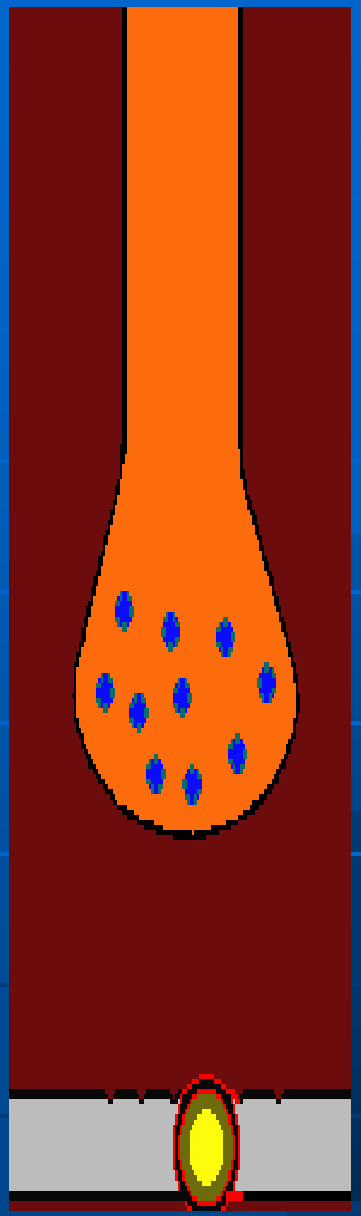
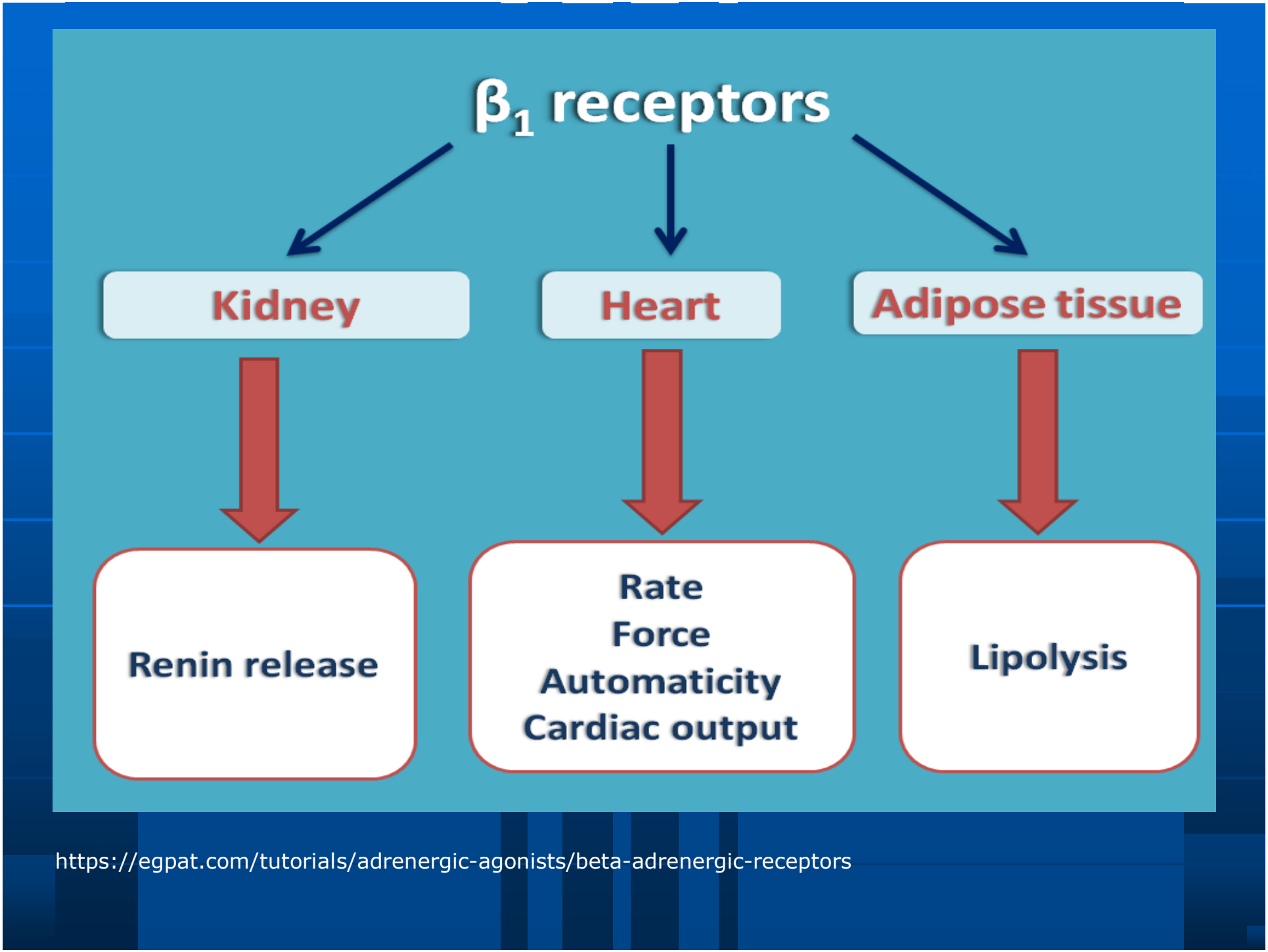
Adrenergic Receptors



Prof.Dr.Nuray Arı, 2018



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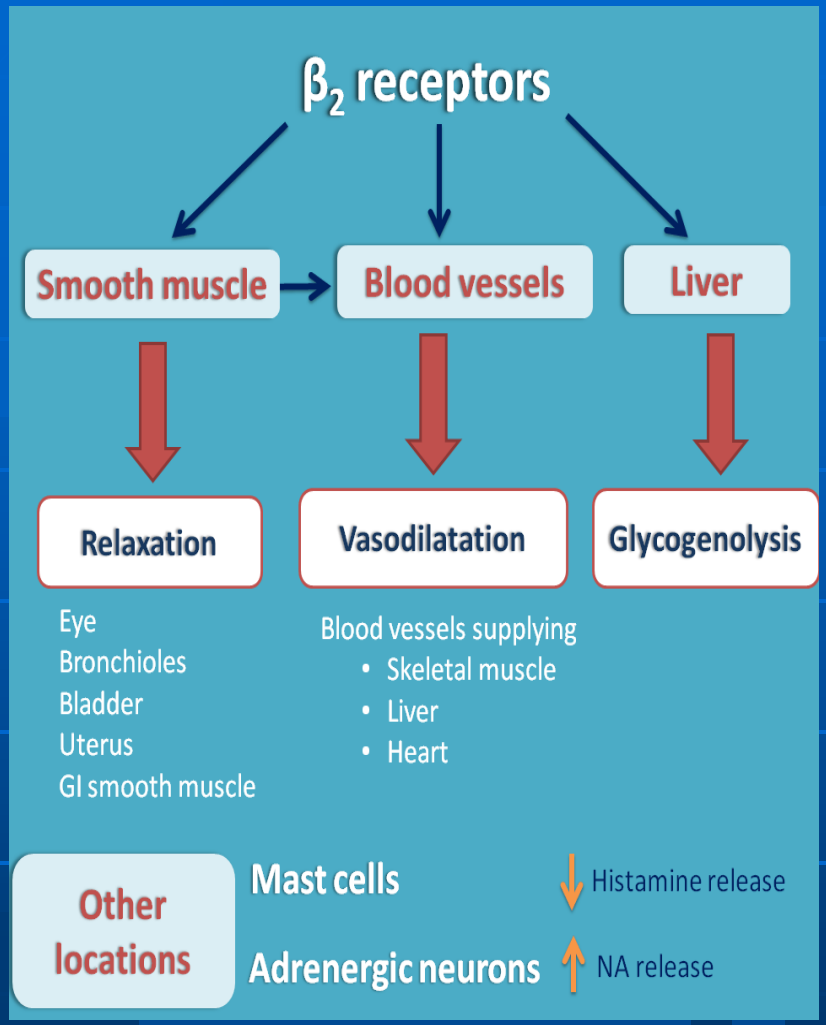

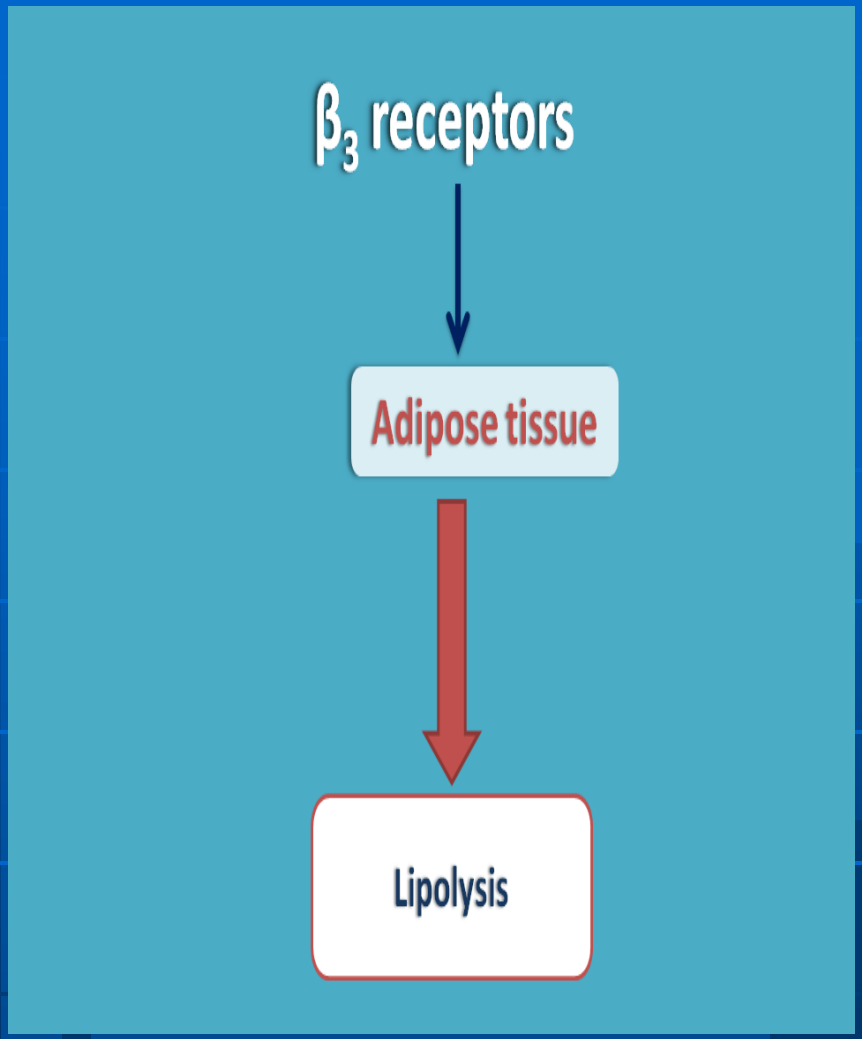

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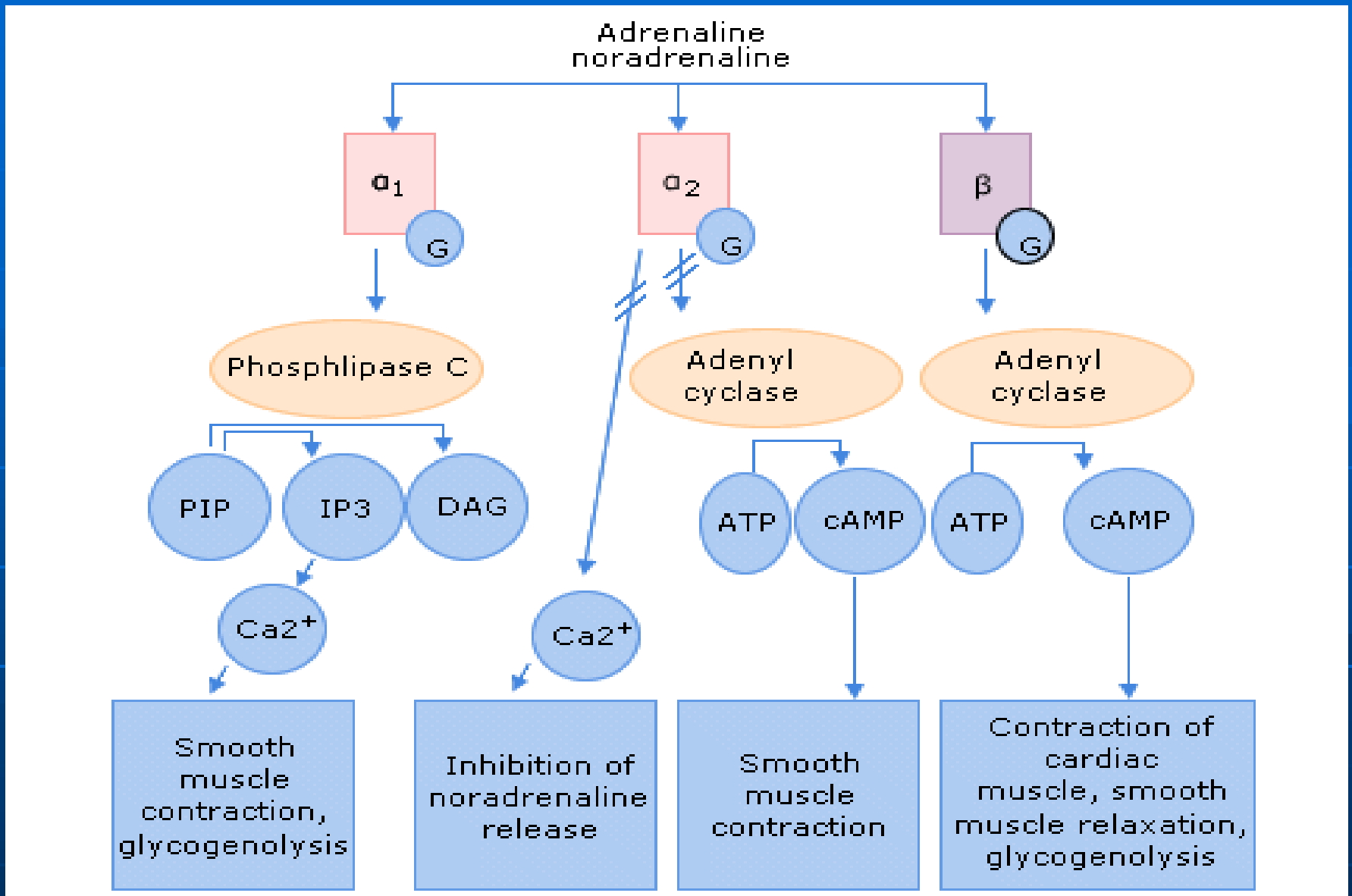
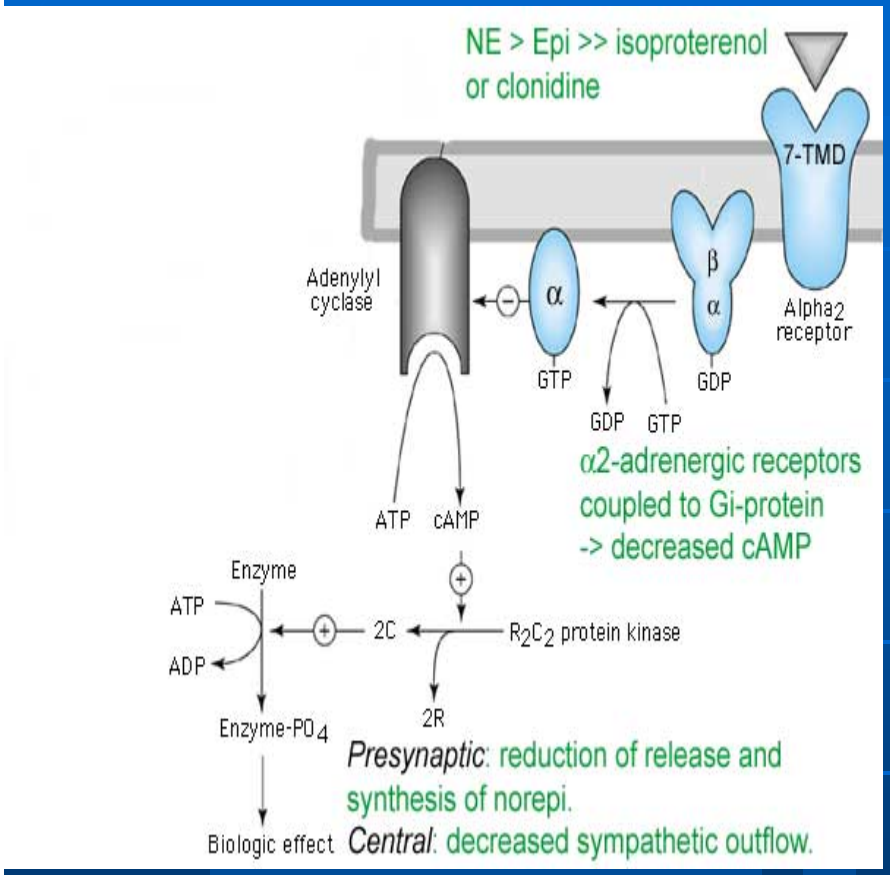
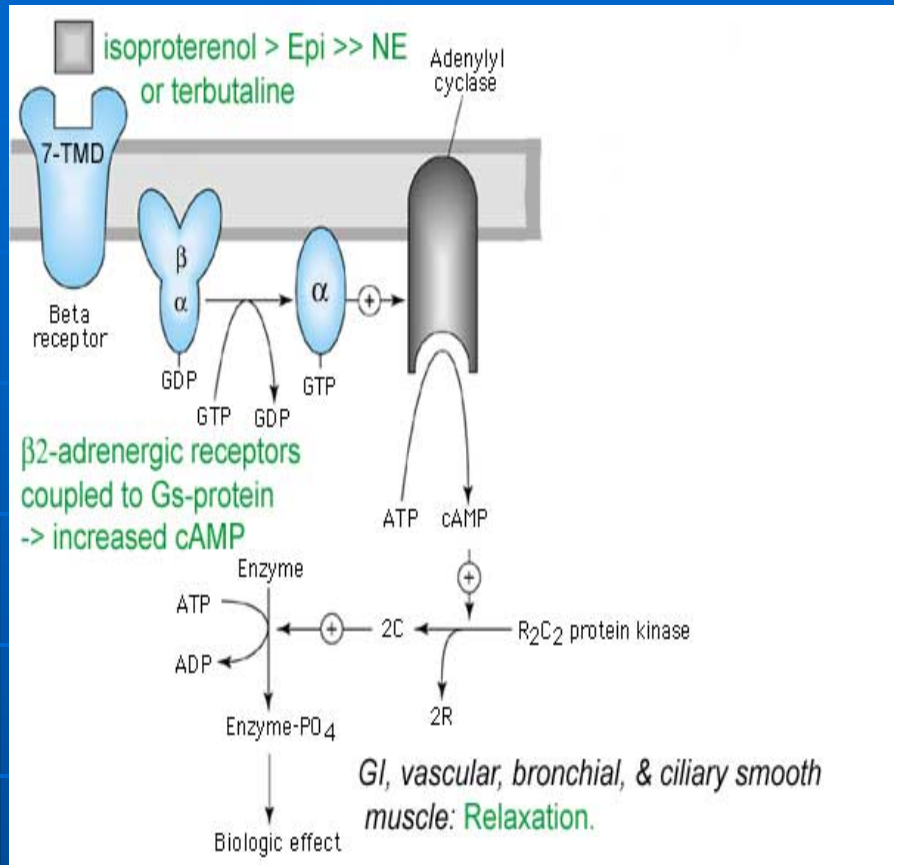
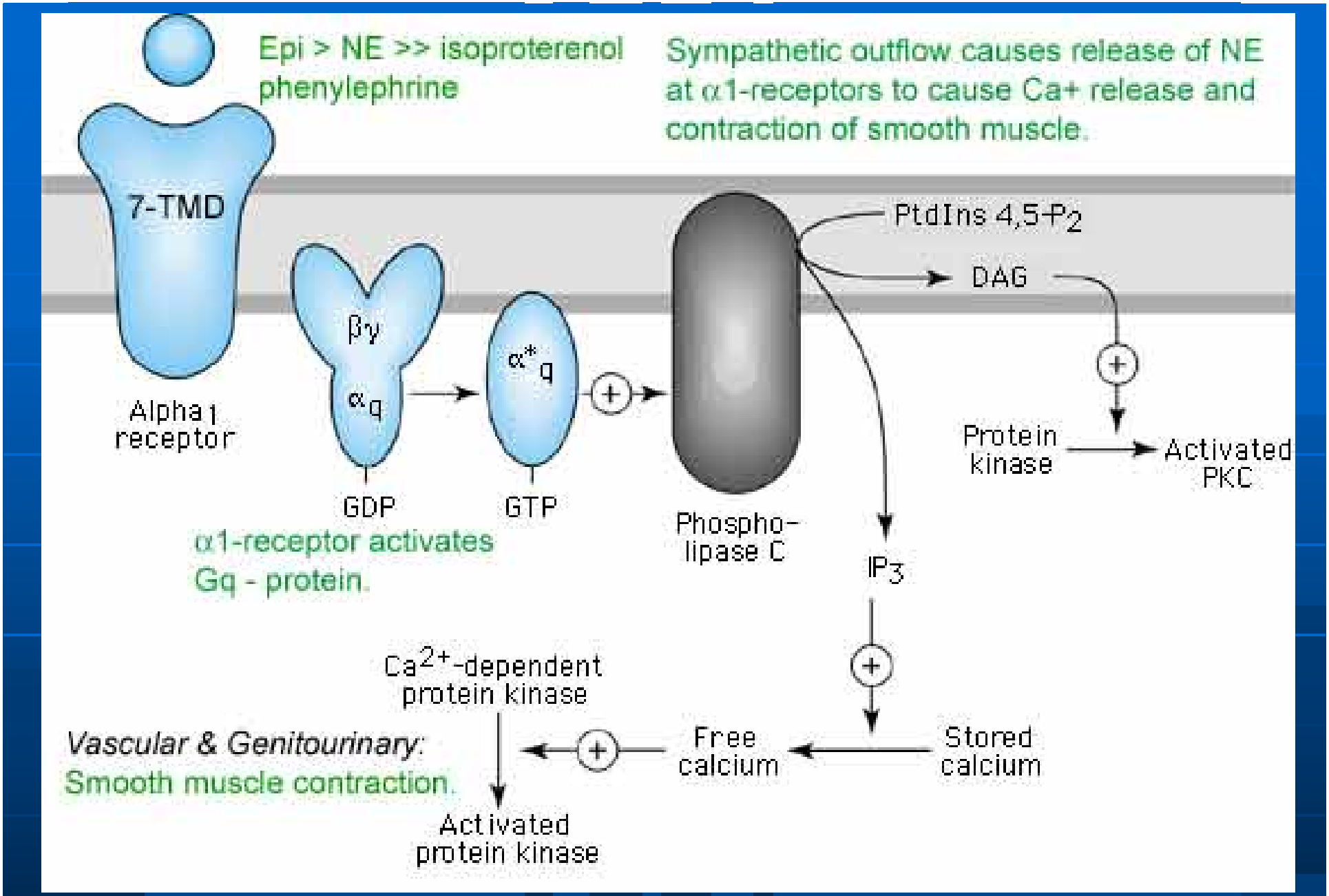


Alpha and beta adrenergic receptors http://www.e-safe anaesthesia.org/sessions/15_05/d/ELFH_Session/561/tab_788.html





http://www-hsc.usc.edu/~bolger/ced/autonomic/Alpha2-Gi.html



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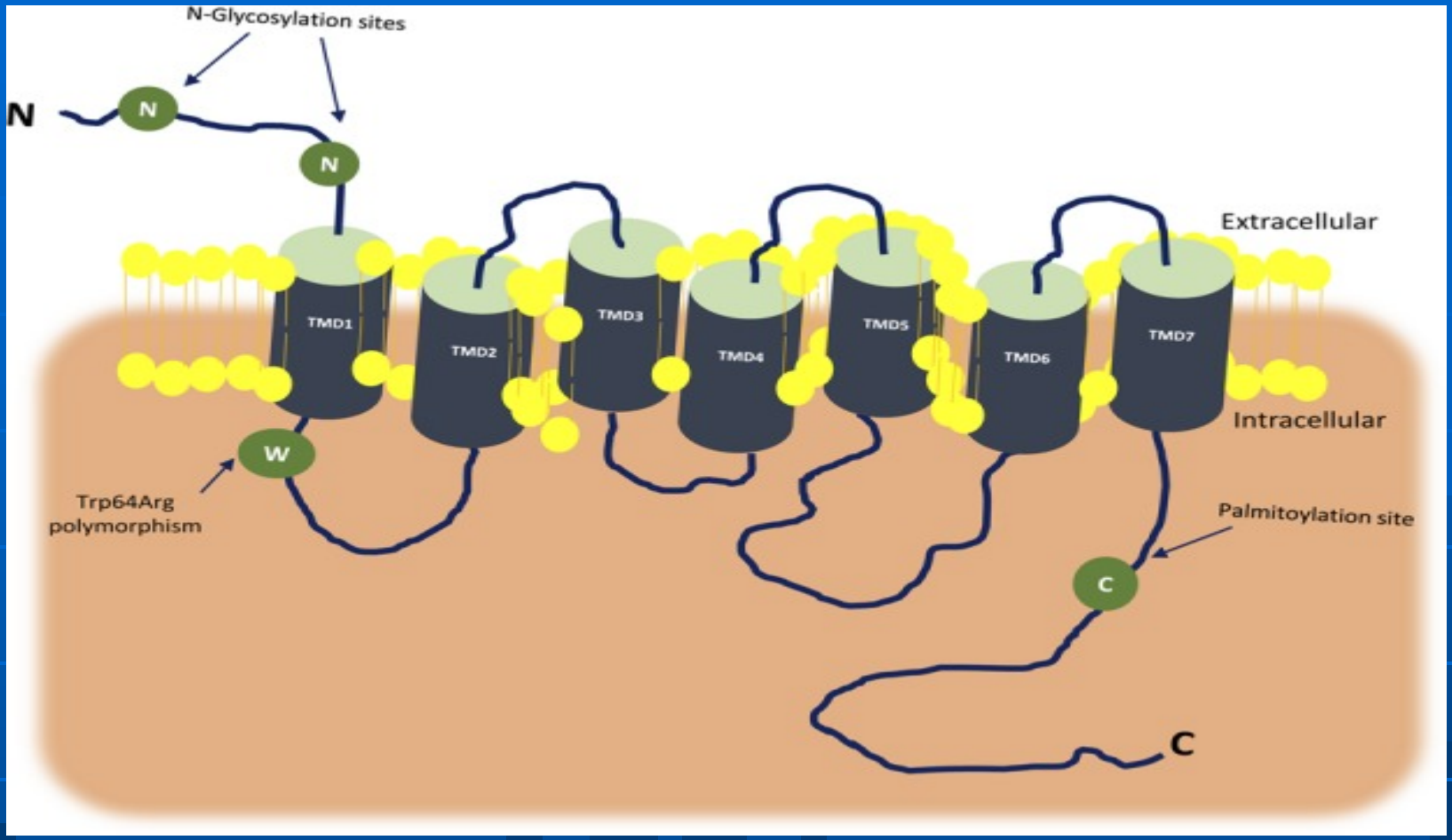
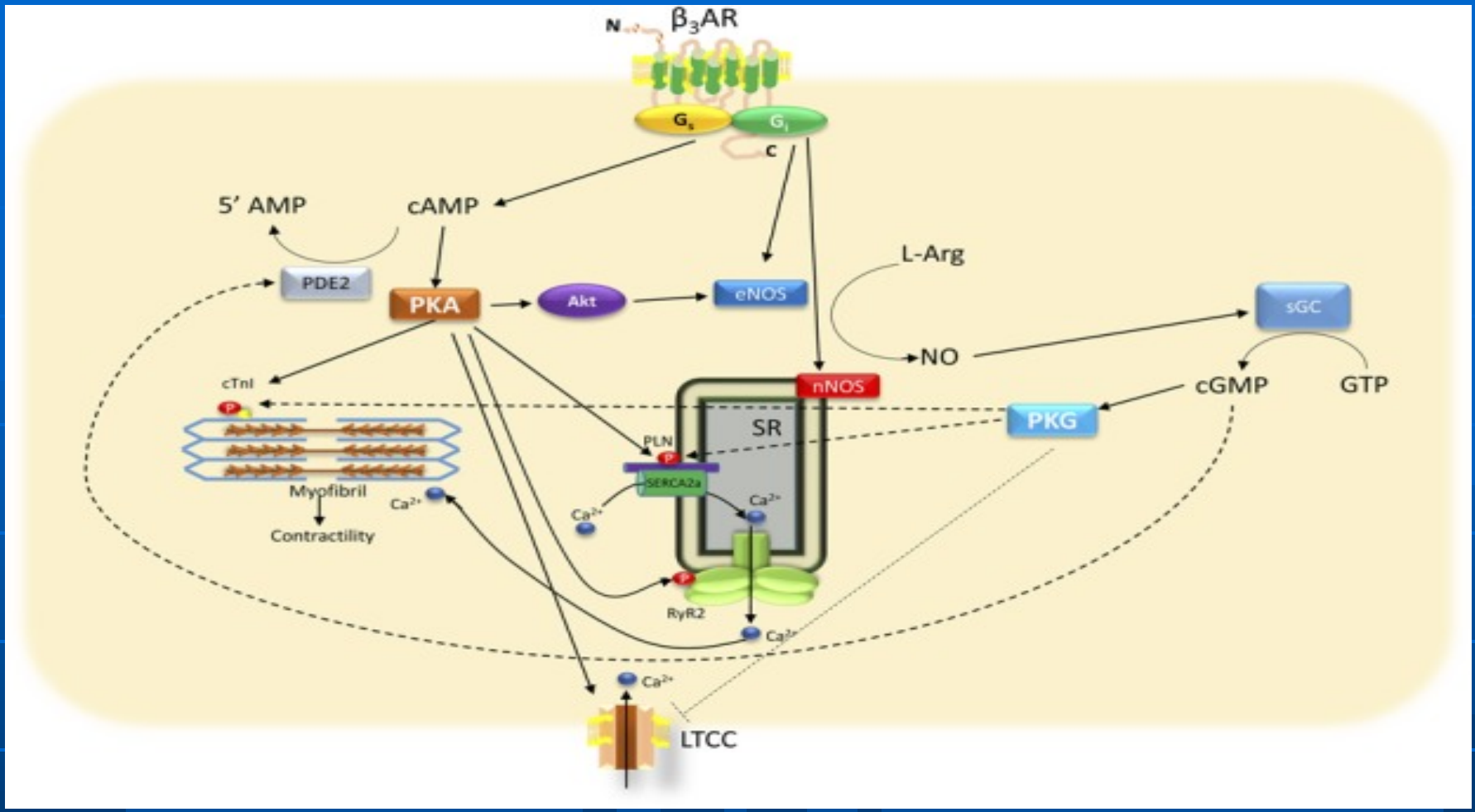


Human β_3AR structure.

The receptor is a GPCR with 7-TMDs, an extracellular N-terminal domain (exD1), and an intracellular C-terminal domain (inD4). The receptor presents also 6 loops, 3 are intracellular (inD1, inD2, and inD3), and 3 are extracellular (exD2, exD3, and exD4). Indicated with arrows are the asparagine (N) residues, in the exD1, that are sites of N-glycosylation; tryptophan (W) in position 64 that is the location of β_3AR-polymorphism (Trp64Arg) and the cysteine (C) in position 361 that is a site subjected to palmitoylation.

Cardiovasc Pharmacol. 2017 Feb; 69(2): 71–78. **Targeting β3-Adrenergic Receptors in the Heart: Selective Agonism and β-Blockade.** Cannavo A, Koch WJ.



β_3AR signaling activation in cardiomyocytes.

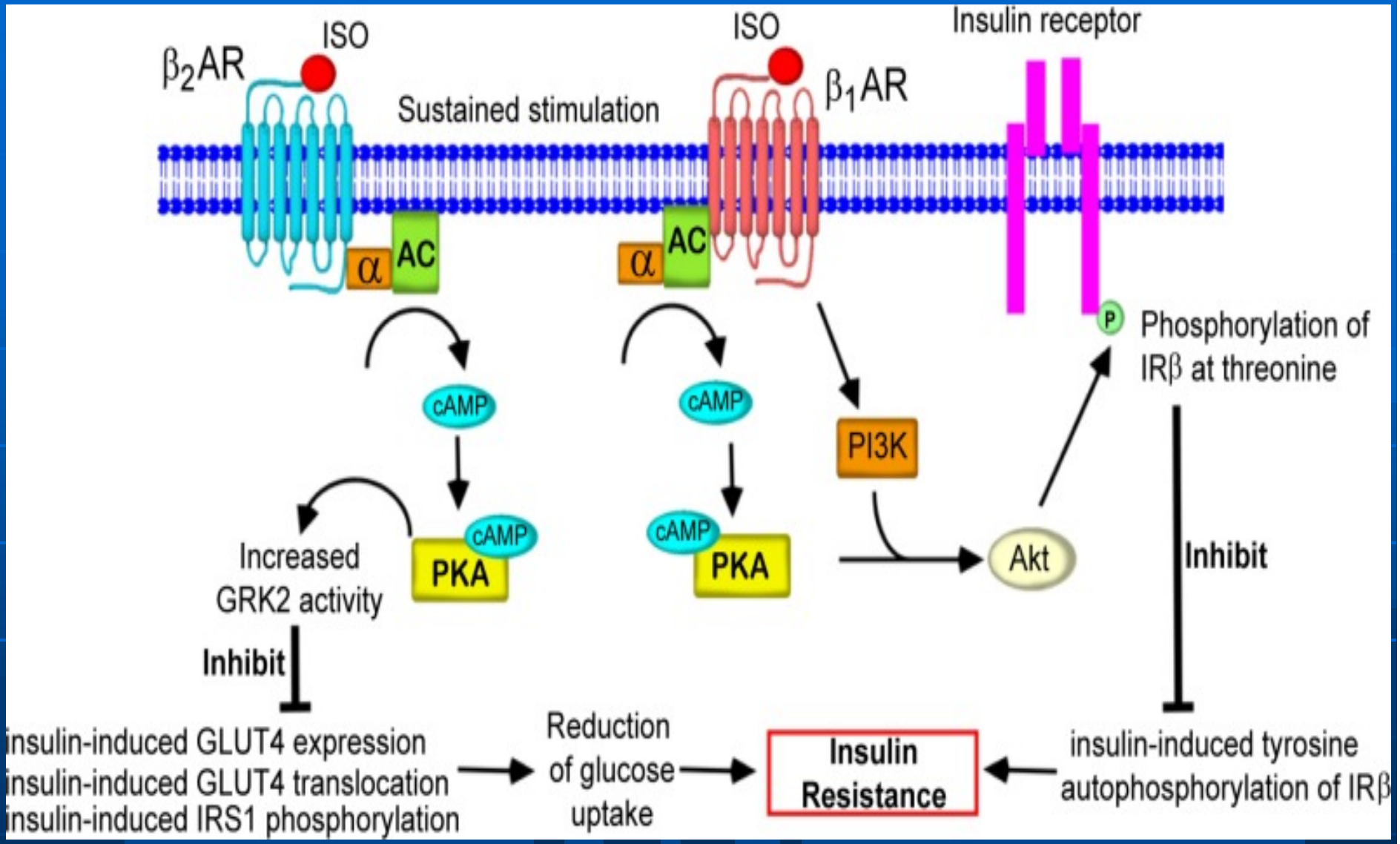
β_3ARs are coupled to both stimulatory G proteins (Gs) and inhibitory G proteins (Gi). Although the Gs pathway induces the generation of cAMP and cGMP which, in turn, activates the PKA and PKG, respectively, the activation of Gi signaling pathway is able to stimulate only the generation of cGMP and the activation of PKG.

J Cardiovasc Pharmacol. 2017 Feb; 69(2): 71–78. **Targeting β3-Adrenergic Receptors in the Heart: Selective Agonism and β-Blockade.** Cannavo A, Koch WJ.

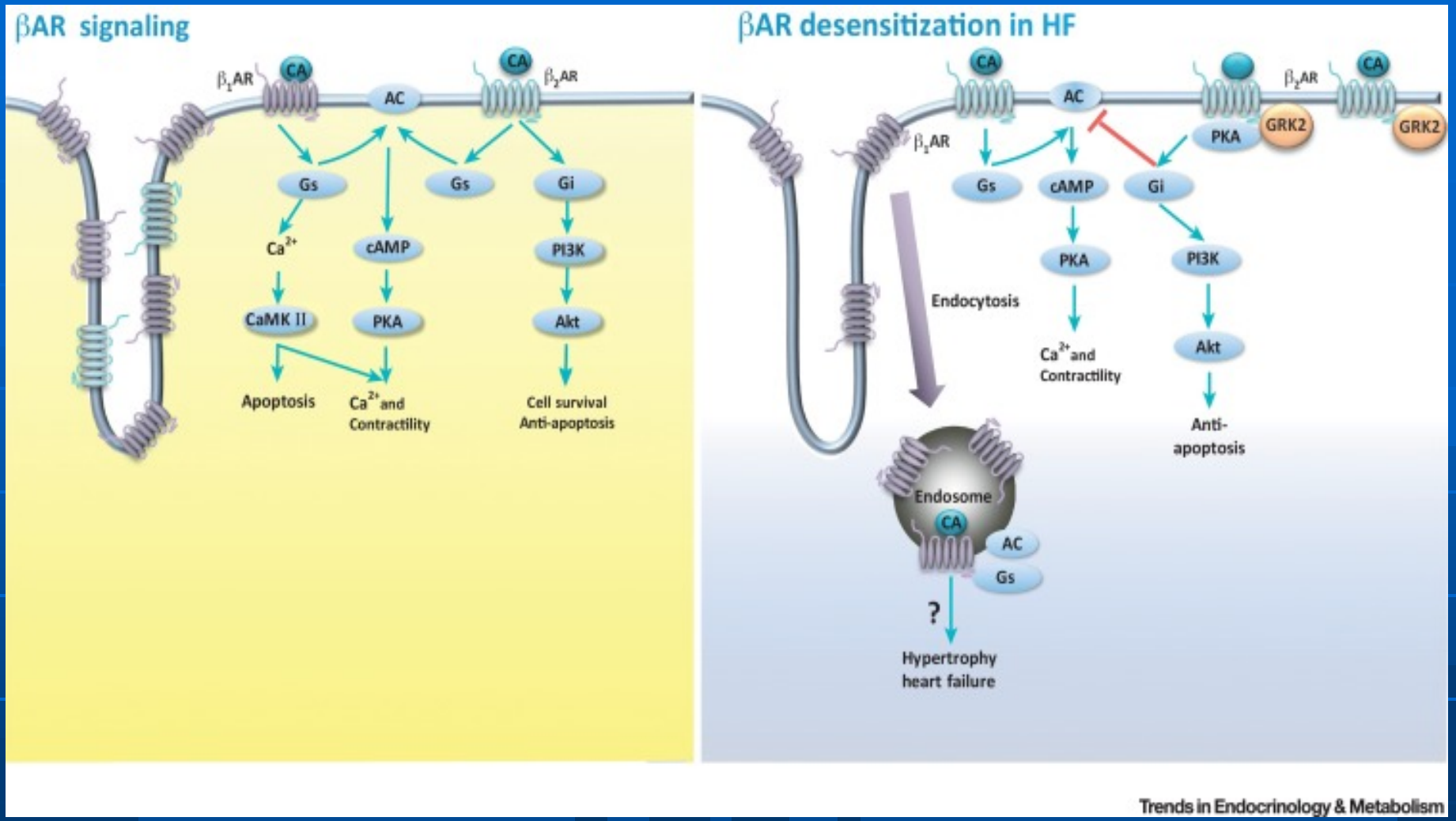
β-Adrenergic Receptor Signaling in the Heart

Sympathetic activation increases cardiac output through the release of catecholamines. The effects of catecholamines on the myocardium are primarily mediated by βAR activation. There are three subtypes of βAR: β_1AR, β_2AR, and β_3AR. In the heart, nonselective βAR stimulation activates the G_s-AC (adenylyl cyclase)-cAMP cascade, leading to PKA-dependent phosphorylation of a set of regulatory proteins involved in cardiac excitation–contraction coupling and energy metabolism, resulting in greater contractility. However, activation of β_2AR can also promote a coupling switch from the G_s to the $G_i$pathway [27]. The coupling of β_2AR to G_i is under the influence of GRK-PKA- and/or -PKC-mediated phosphorylation [85]. The β_2AR-$G_i$signaling pathway has a crucial role in the regulation of cell proliferation and protection against cardiomyocyte apoptosis via transactivation of a PI3K-Akt signaling pathway. The β_2AR-G_i signaling pathway also attenuates the βAR-G_s-mediated inotropic response via inhibition of AC activity [86]. Meanwhile, adrenergic signaling also activates PKA and Akt to promote glucose uptake in the heart [10,11]. These shared cellular functions suggest that insulin signaling and adrenergic signaling converge in the heart.

Insulin and β Adrenergic Receptor Signaling: Crosstalk in Heart. *QinFu et al.* Trends Endocr Metab., Volume 28, Issue 6, 2017, Pages 416-427

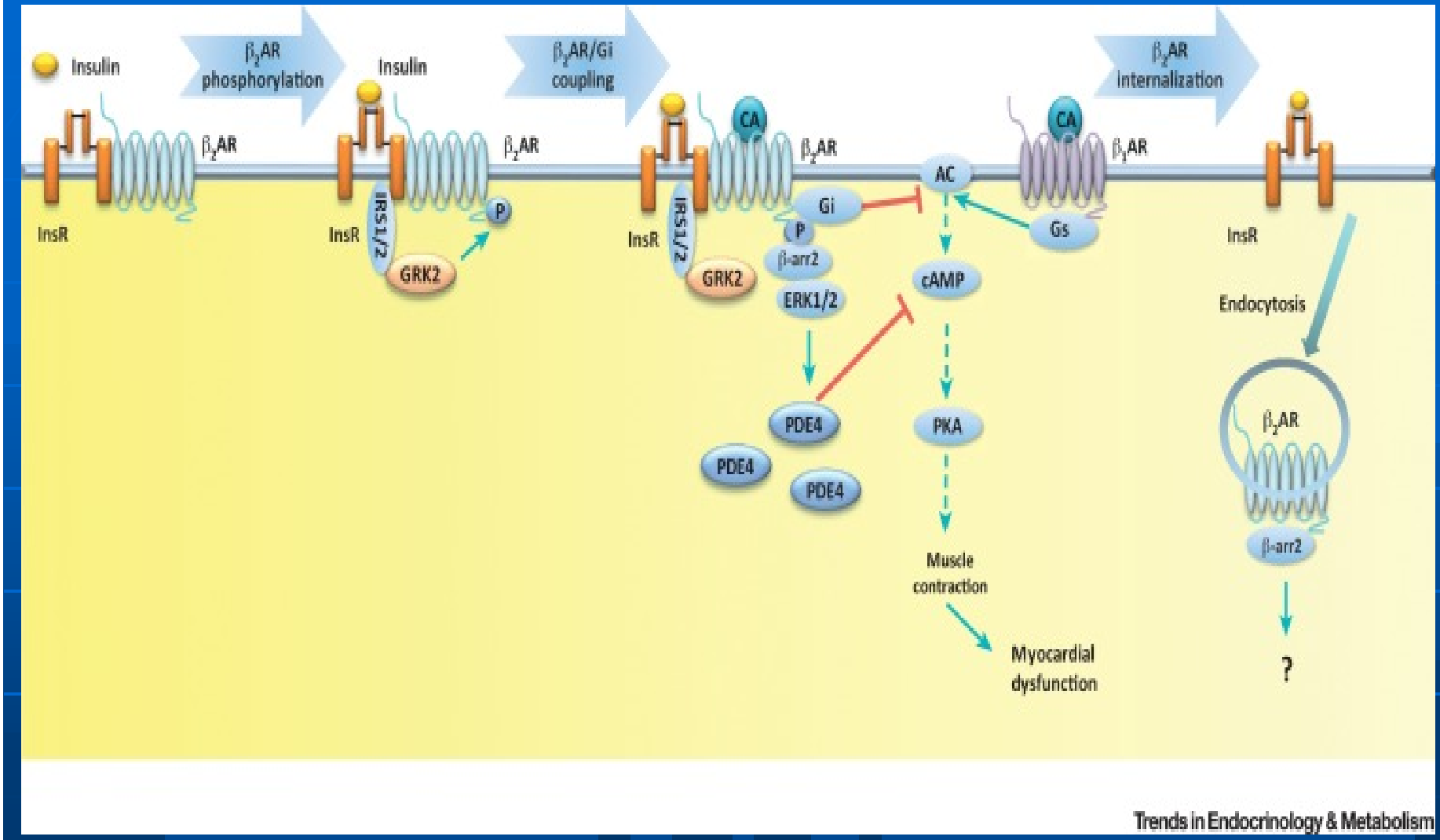


the signaling pathway for βAR-mediated cardiac insulin resistance *Biomol Ther (Seoul). 2017 Jan; 25(1): 44–56. Mangmool S et al*



β-Adrenergic Receptor (βAR) Signaling and Desensitization in Heart Failure

Trends Endocr Metab., Volume 28, Issue 6, June 2017, Pages 416-427 Insulin and β Adrenergic Receptor Signaling: Crosstalk in Heart. QinFu et al.



Insulin Induces β-Adrenergic Receptor (βAR) Desensitization in the Heart.

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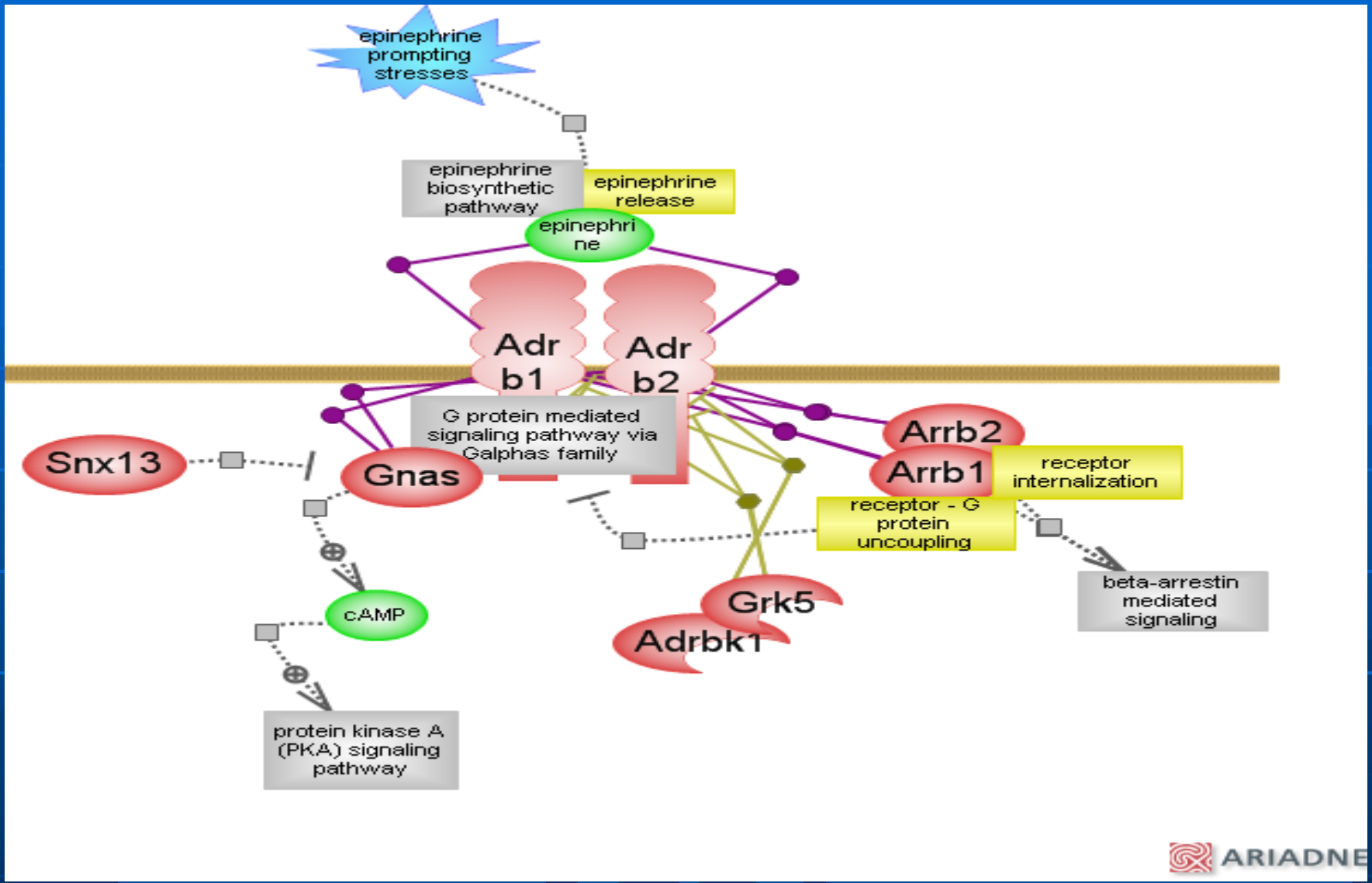
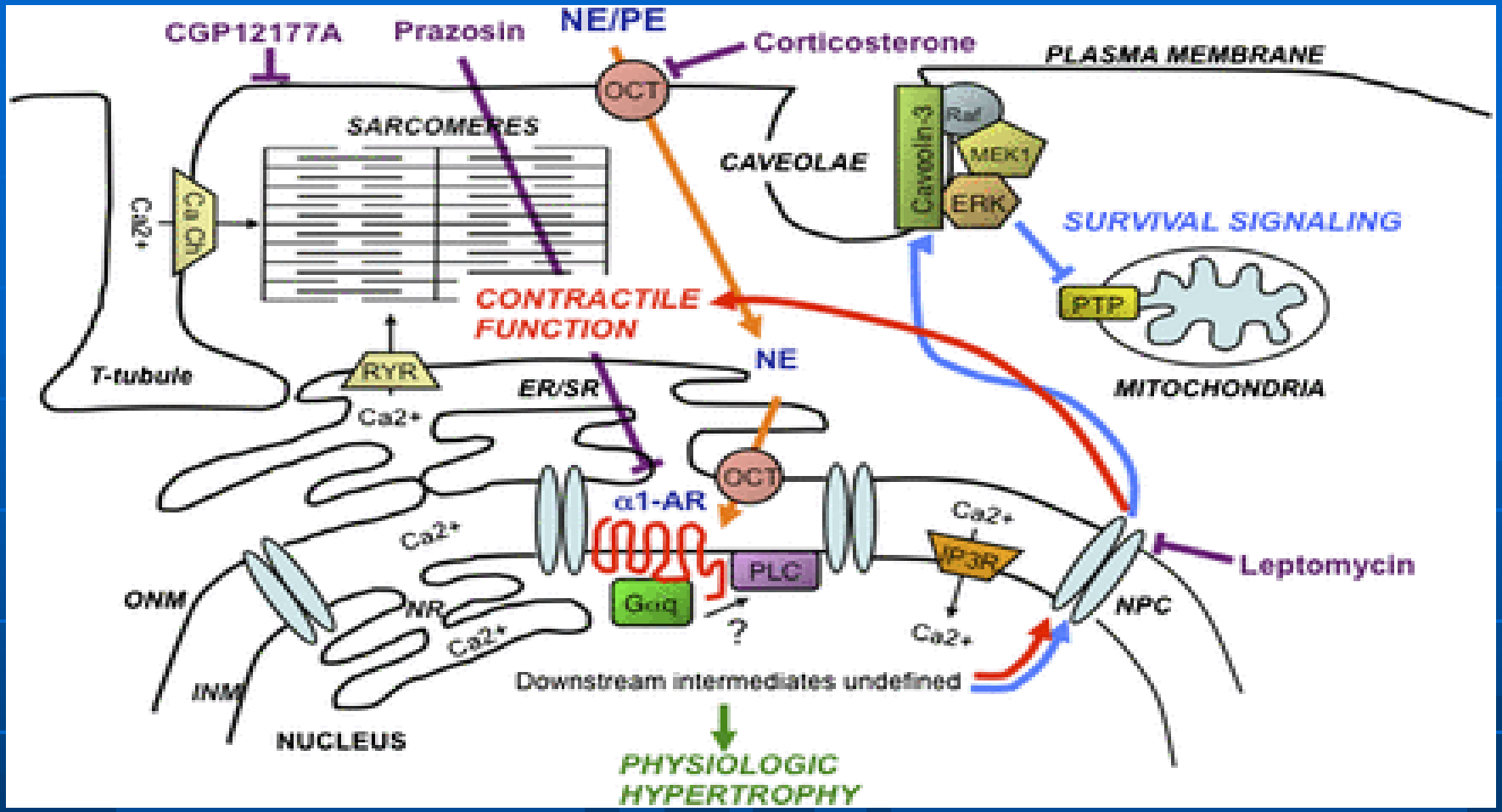


https://rgd.mcw.edu/rgdweb/pathway/pathwayRecord.html?processType=view&species=Rat&acc_id=PW:0000794



Model for α_1-AR signaling at the nuclear membrane.

In adult cardiac myocytes, catecholamine α_1-AR agonists (NE/PE) are actively transported into the myocyte via organic cation transporter 3 (OCT), which can be inhibited by corticosterone. Cardiac Alpha$_1$-Adrenergic Receptors: Novel Aspects of Expression, Signaling Mechanisms, Physiologic Function, and Clinical Importance

Timothy D. O'Connell, Pharmacological Reviews January 2014, 66 (1) 308-333;