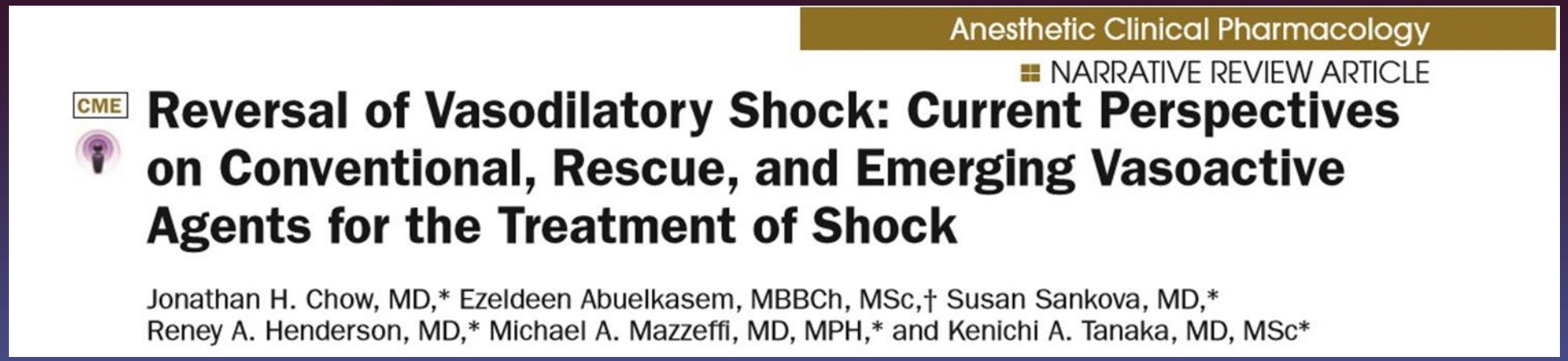
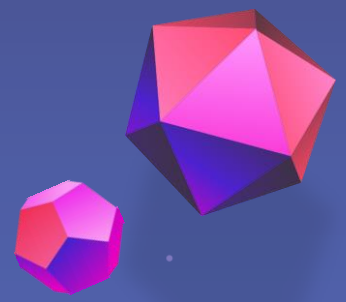


Hot Topic
Reversal of Vasodilatory Shock: Current Perspectives on Conventional, Rescue, and Emerging Vasoactive Agents for the Treatment of Shock

R1ภัควิภา/อ.เอกสักก์

Anesth Analg 2020 January

OUTLINE



INTRODUCTION

In operation room , vasodilation is also frequently encountered aft er induction of general anesthesia and administration of neuraxial local anesthetics

Treating hypotension is critical in preventing adverse outcomes

Several pharmacological interventions are available to rapidly treat hypotension due to vasodilation , different mechanisms and distribution of target receptors

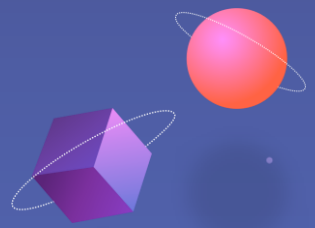
TYPE OF SHOCK

01.
Distributive

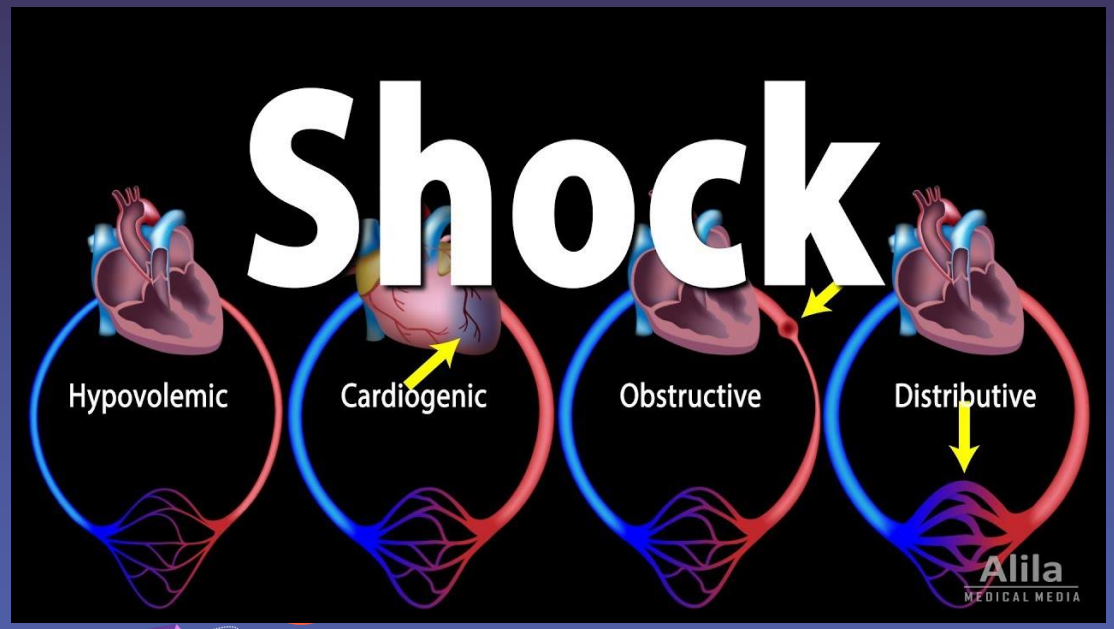
02.
Cardiogenic

03.
Obstructive

04.
Hypovolemic

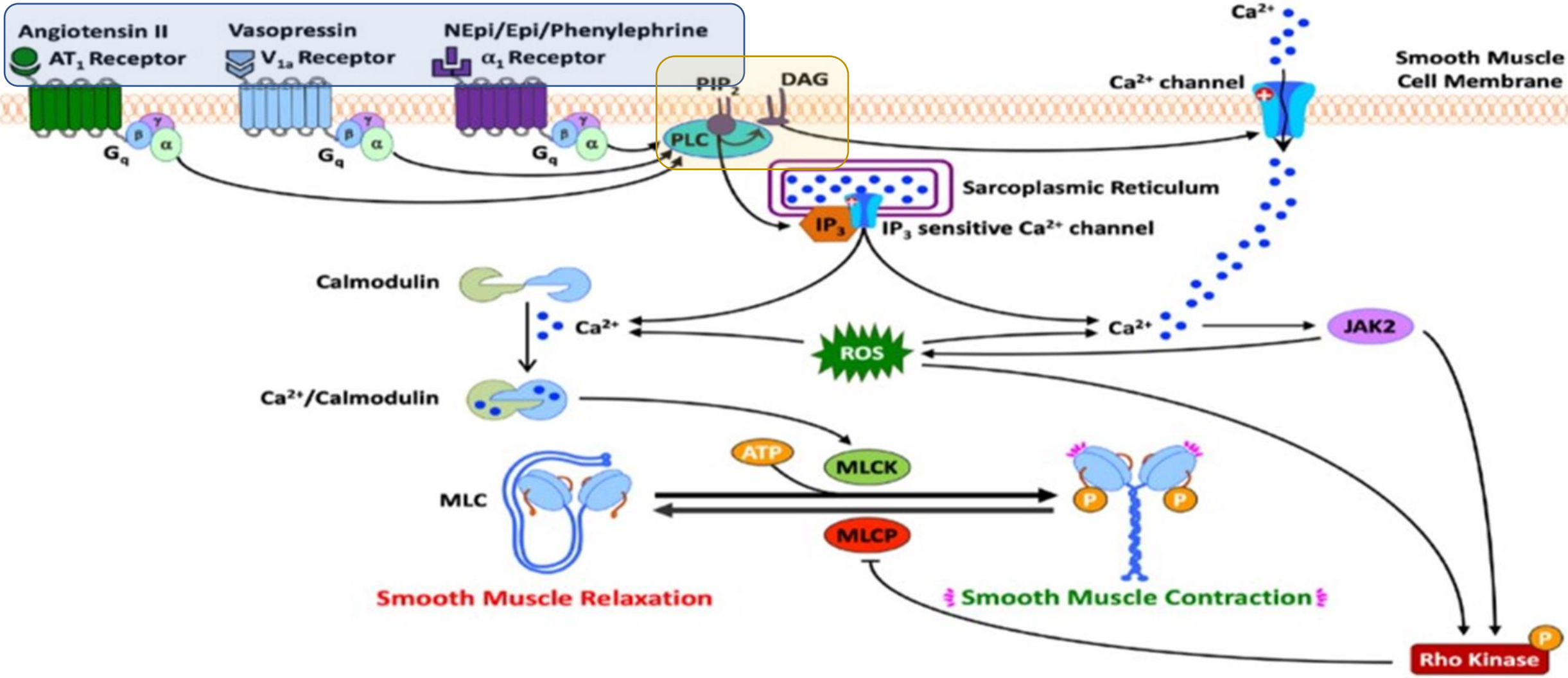


TYPE OF SHOCK

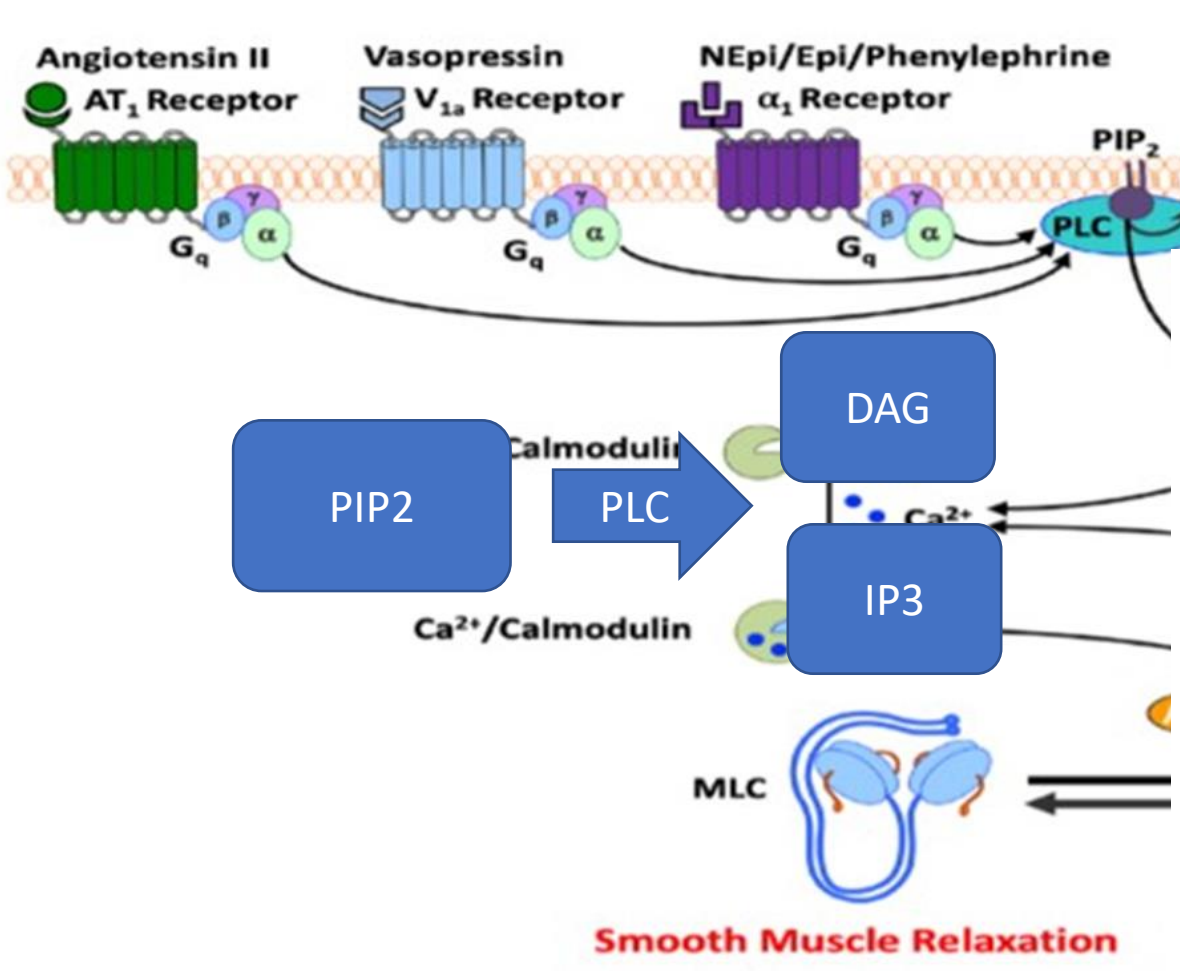


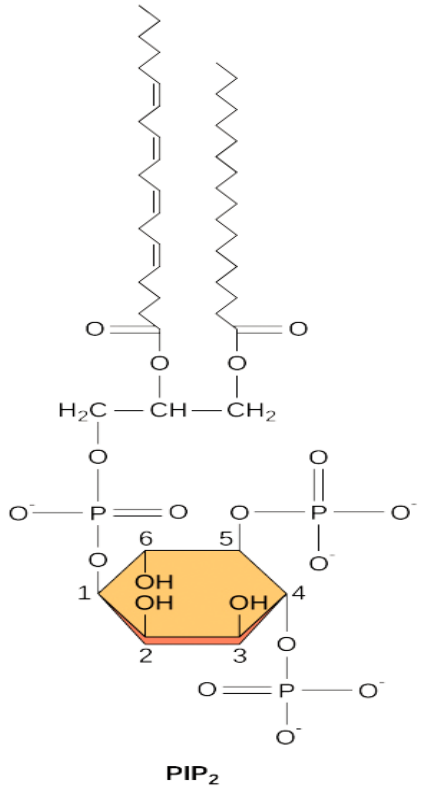
	Preload	Cardiac output	afterload
Hypovolemic	↓	↓	↑
Cardiogenic	↑	↓	↑
distributive	↓/-	↑	↓
obstructive	↑	↓	-/↑

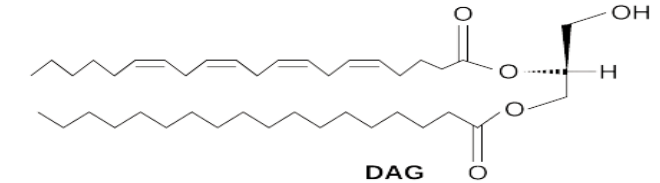
Mechanism of vasoconstriction

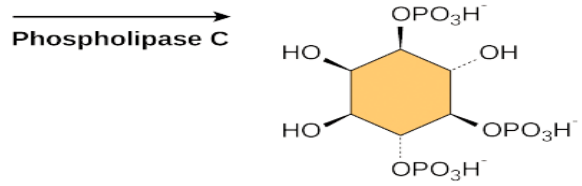


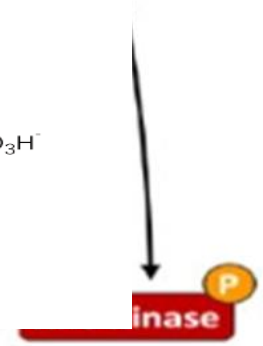
Mechanism of vasoconstriction



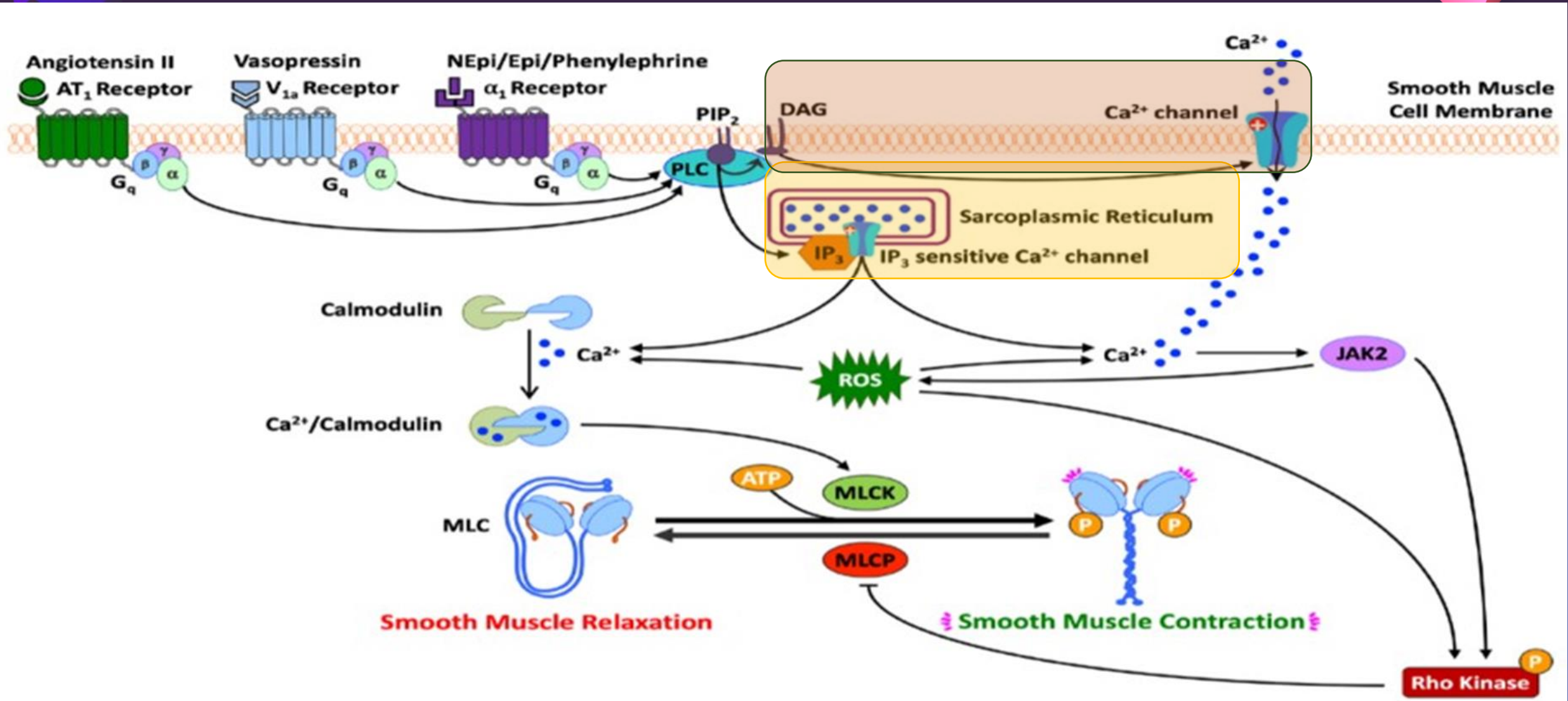




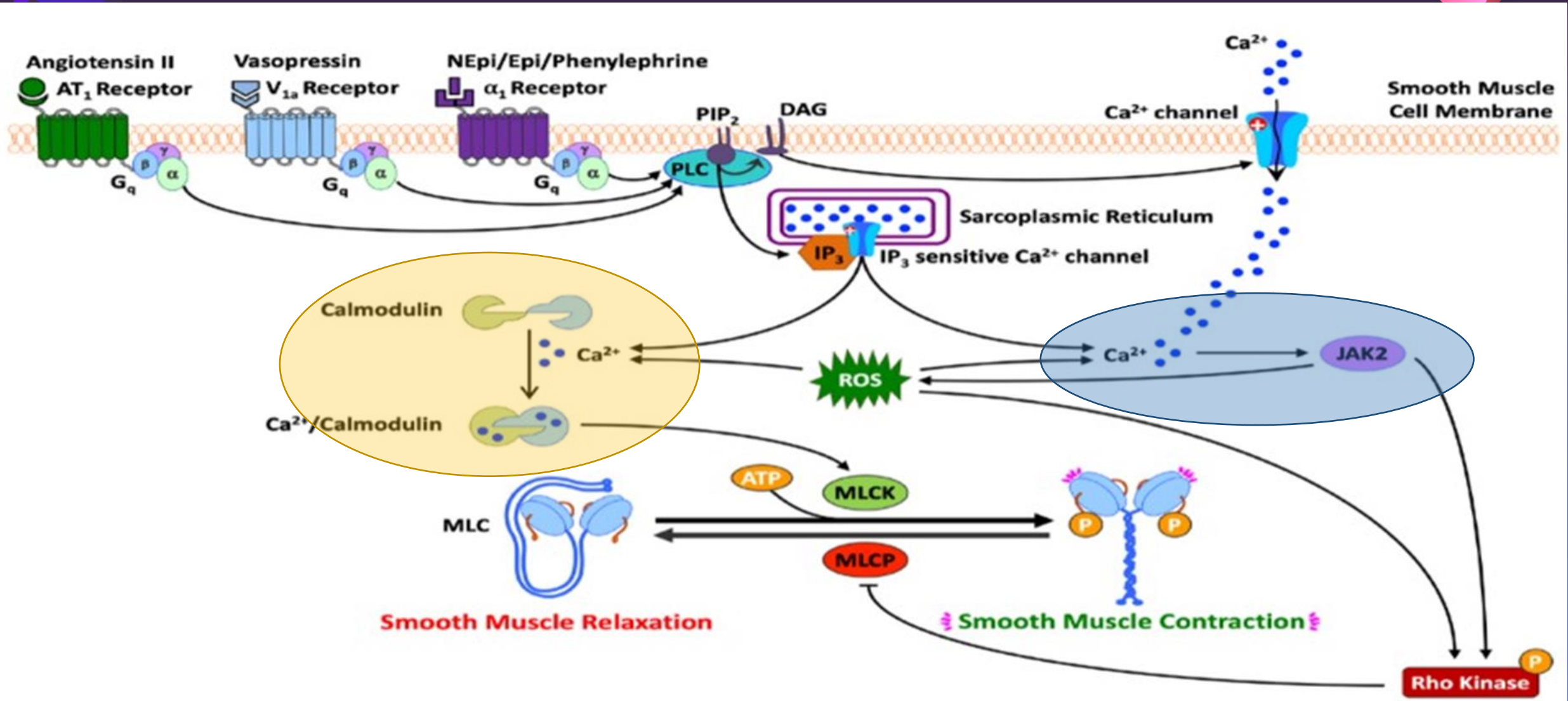




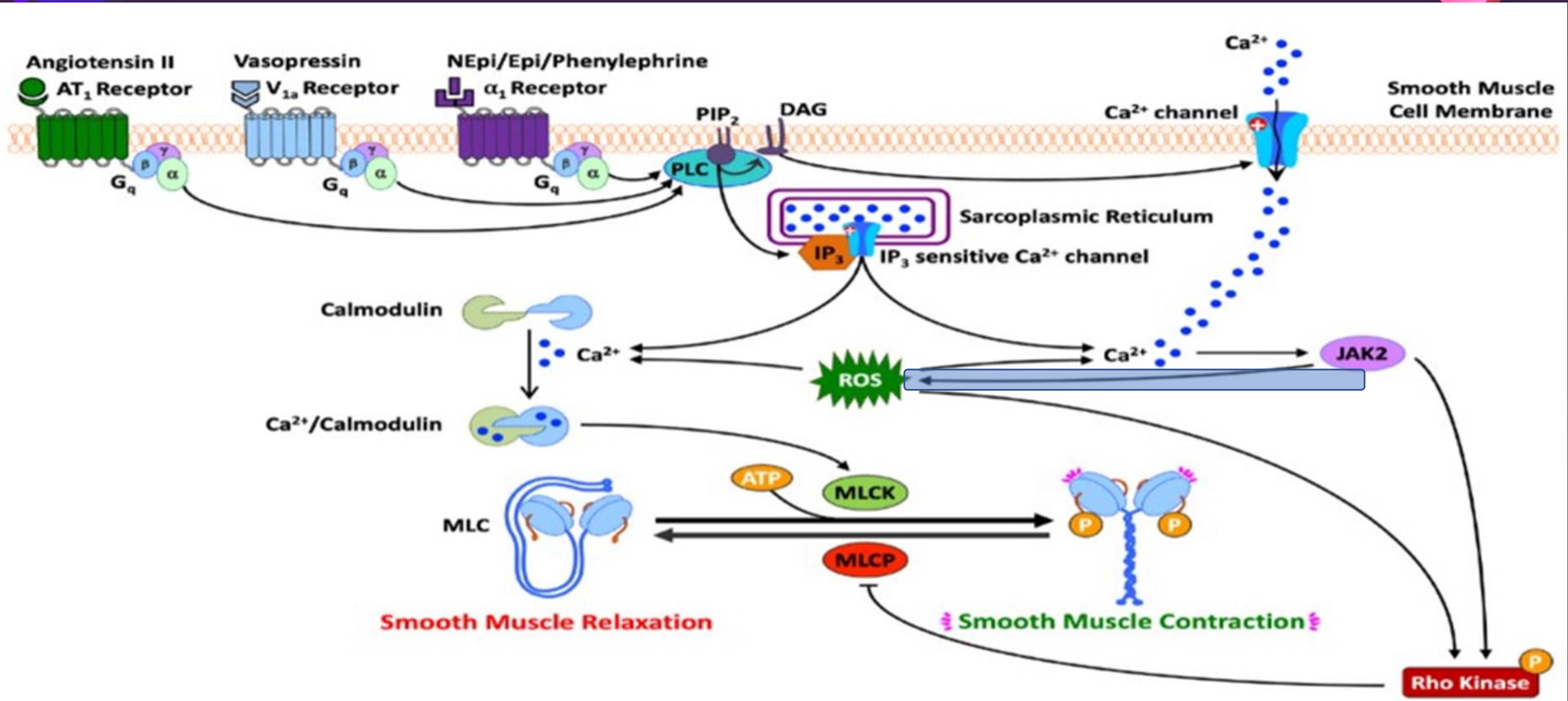
Mechanism of vasoconstriction



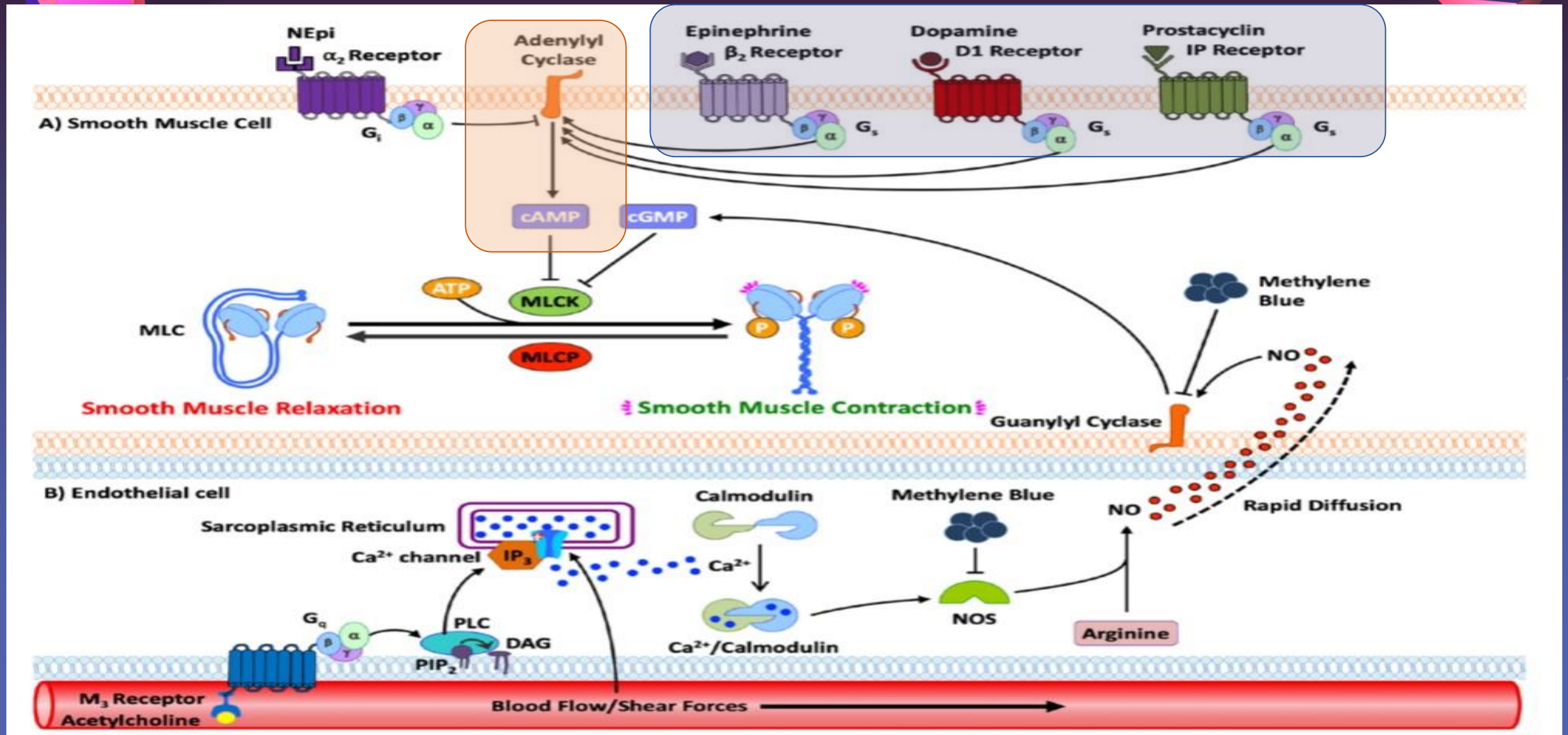
Mechanism of vasoconstriction



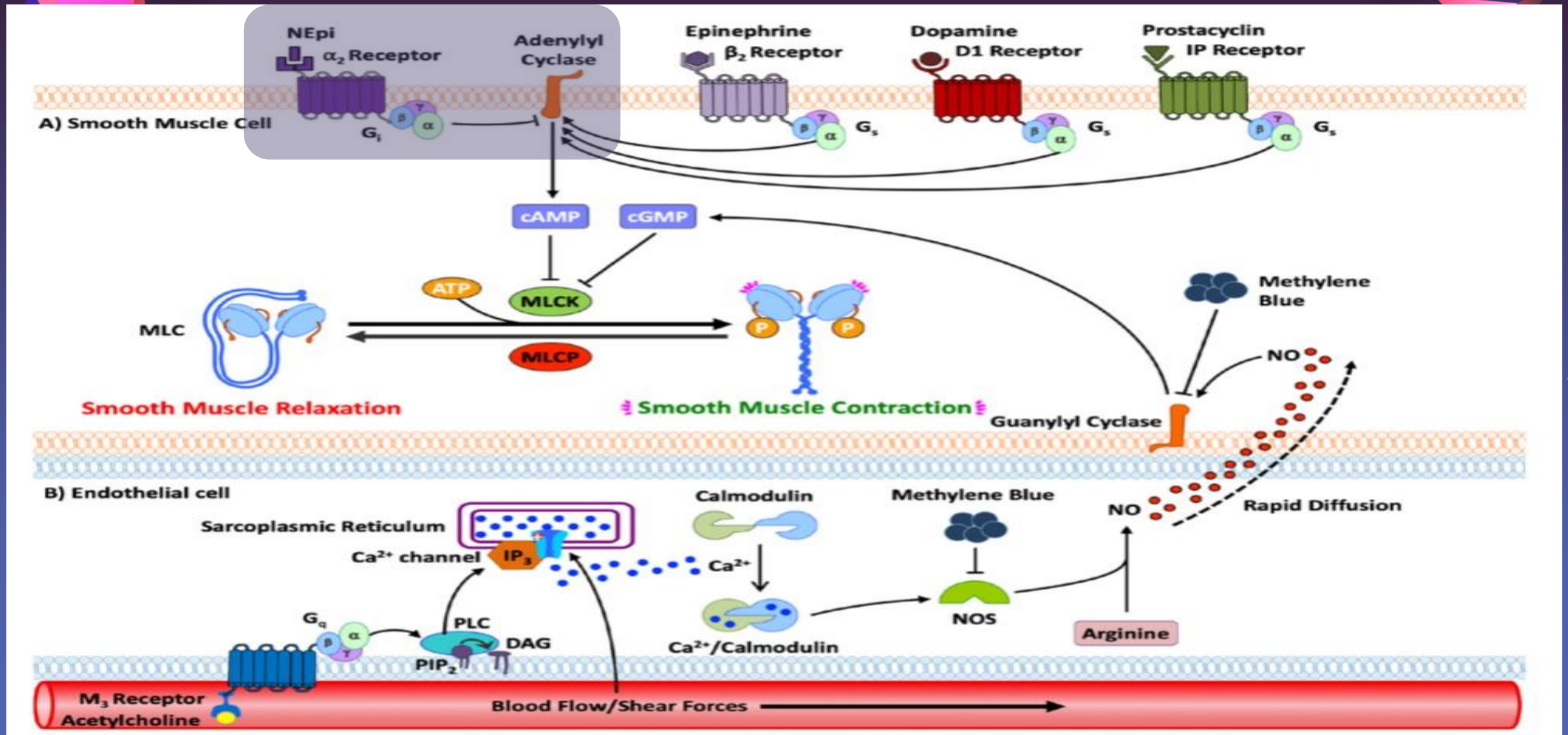
Mechanism of vasoconstriction



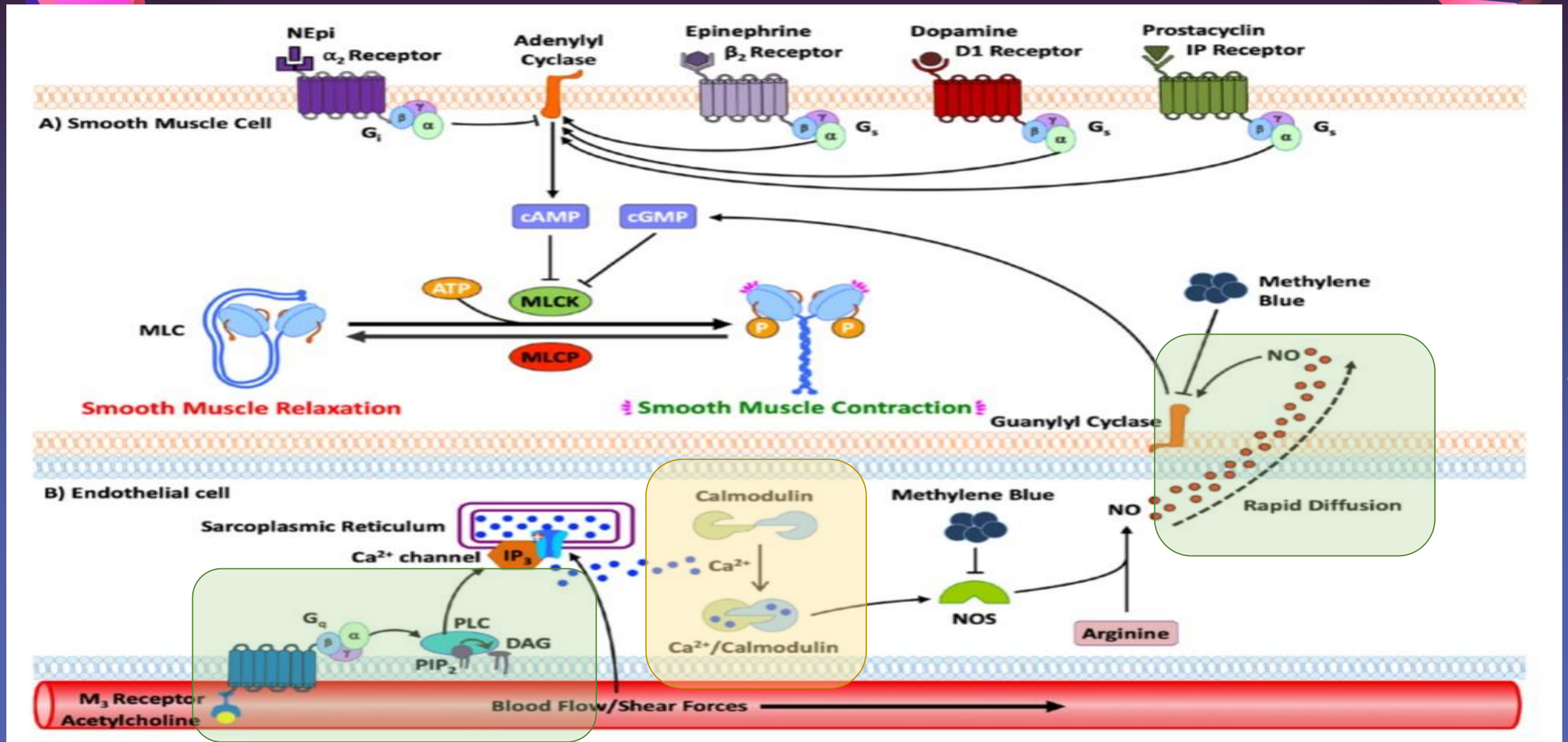
Mechanism of vasodilation



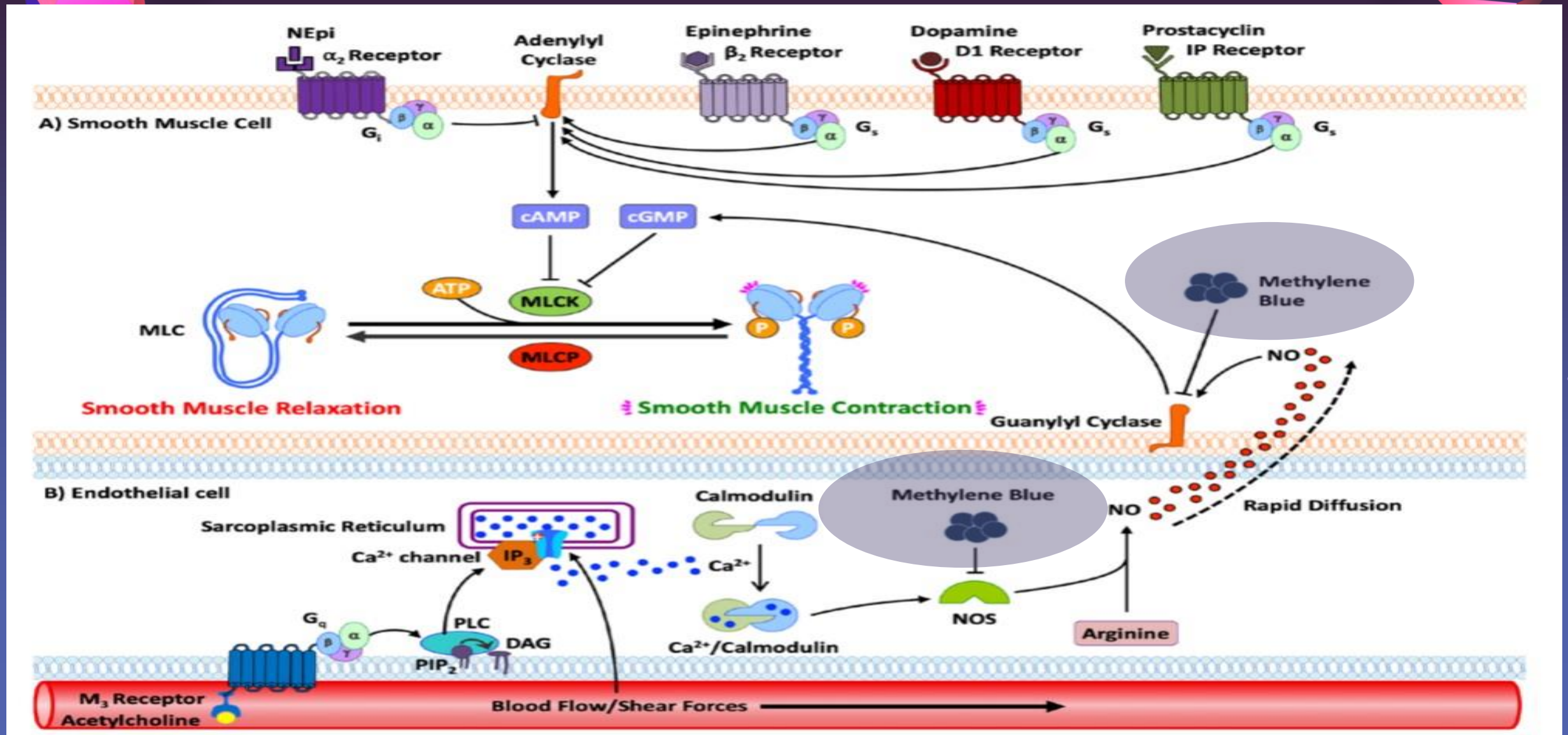
Mechanism of vasodilation



Mechanism of vasodilation



Mechanism of vasodilation



Vasoactive agent

Norepinephrine

The 1st line agent for the treatment of vasodilatory shock

Endogenous sympathetic hormone

Vasoconstrictor effect are mediated by agonism of “α1 receptors”

Norepinephrine

High dose

Increase pulmonary vascular resistance
Increase myocardial workload
Severe hypertension
Systemic vasoconstriction
Impair perfusion of the mesentery
Organ dysfunction
Metabolic acidosis

Norepinephrine

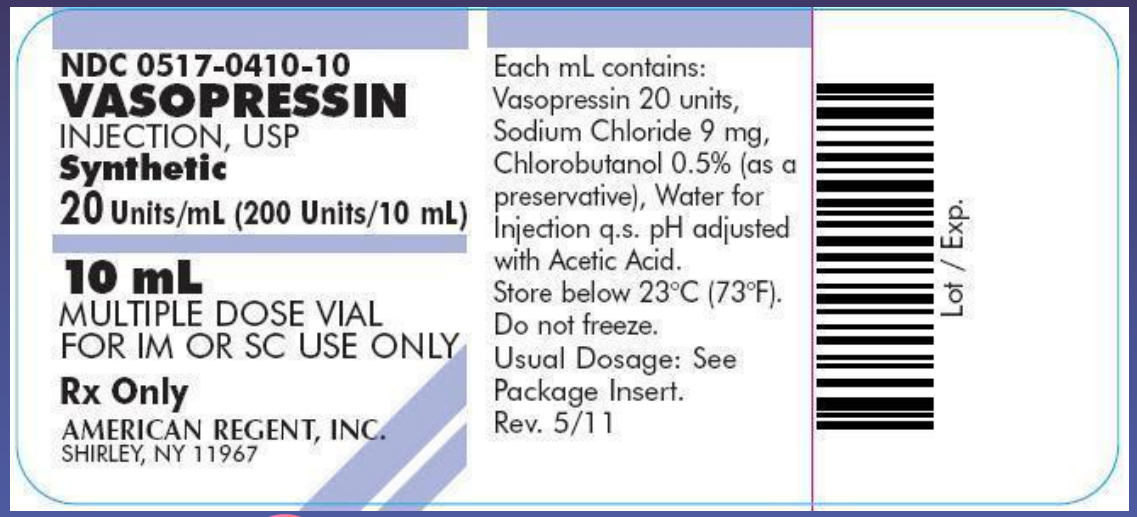
Clinical use

Initial dose 0.08-0.12 mcg/kg/min

No study has detect dosing difference in the elderly population

Desensitization and tachyphylaxis from phosphorylation and internalization of α1 receptors

Vasopressin

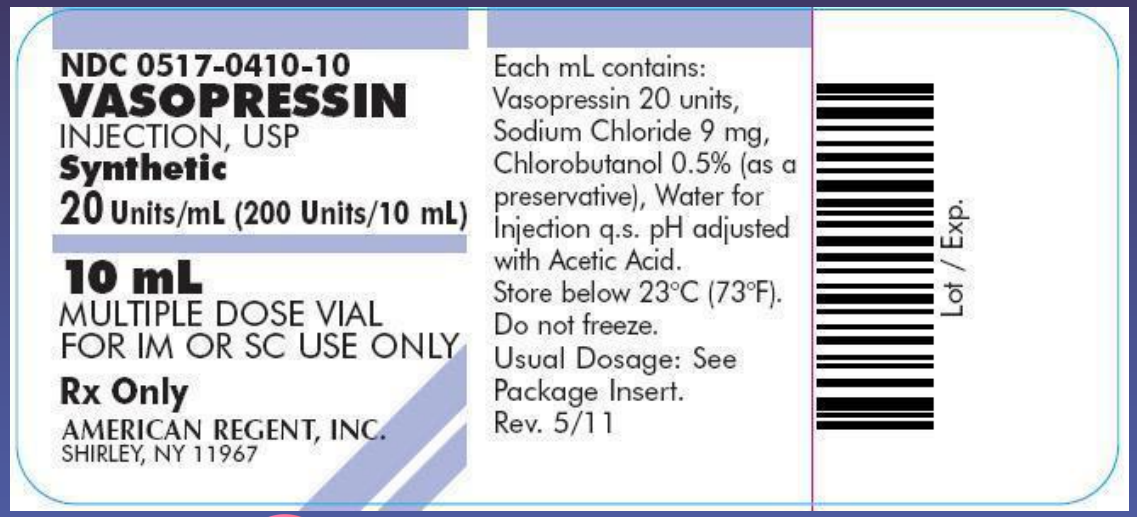


2nd line agent

Vasoconstrictor effect are mediated by agonism of “V1a receptors”

Endogenous peptide hormone synthesized

Vasopressin

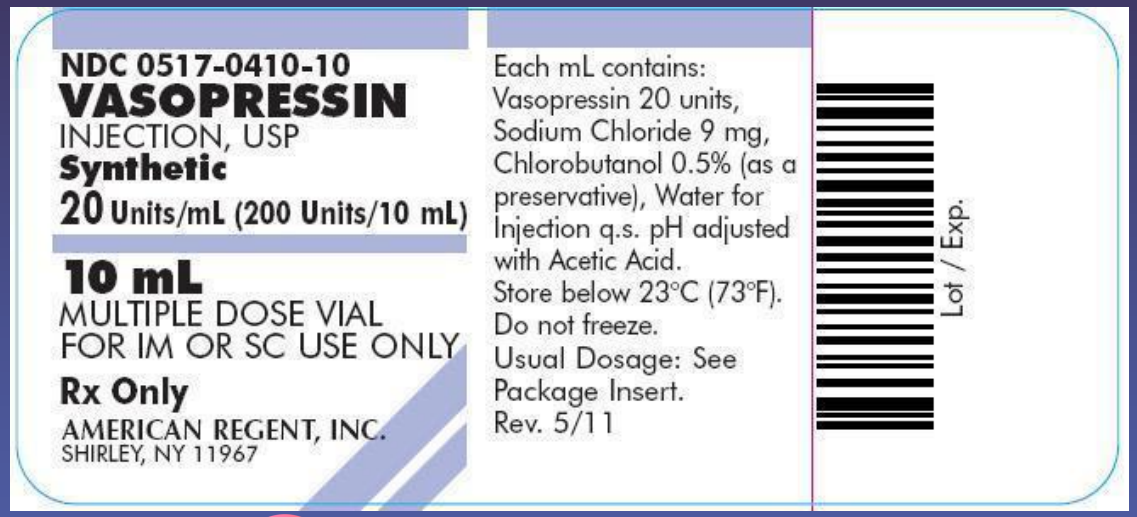


V1 receptor : vascular and mesenteric vasoconstriction

V2 receptor : retention of free water and release of VWF , factor VIII , tissue plasminogen activator , vasodilation

V3 receptor : increase adrenocorticotropic hormone production

Vasopressin



Recommended rate 0.03 u/min

> 0.03 u/min associated with cardiac and mesenteric ischemia

No study has detect dosing difference in the elderly population

Start vasopressin early when NE > 0.15 ug /kg/min

Vasopressin

Synthetic analogues

Terlipressin : V1 , V2 receptor
Long half life 4-6 hr
Superior to vasopressin in septic shock
Limit to give bolus medication during vasodilatory shock

Selepressin : selective V1 receptor

Epinephrine

3rd line agent

Endogenous sympathomimetic catecholamine

Vasoconstrictor effect are mediated by stimulation of “α1 receptors”

Epinephrine

Higher affinity for β2 receptors > α1 receptors

Dose dependent

2-10 ug/min	>10 ug/min
Low to moderate dose	**Higher dose**
β2 receptors : ↑ inotrope ↓ SVR	α1 receptors : ↑ SVR , MAP

Phenylephrine

Not recommended for the routine management of septic shock

Important role in the management of other forms of vasodilatory shock

Exogenous selective “α1 agonist”

Increase venous return and cause reflex bradycardia secondary to systemic vasoconstriction

Phenylephrine

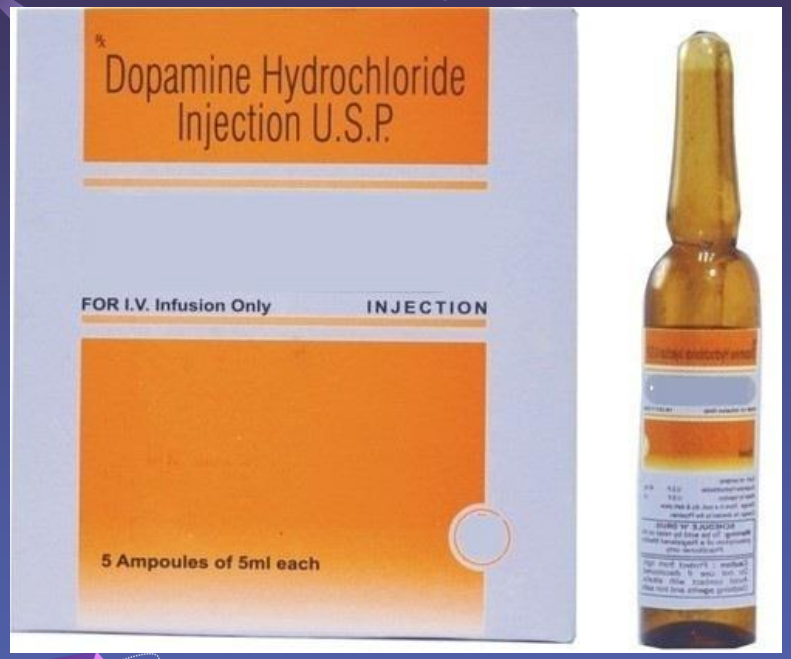
Routine used in the perioperative setting for the short-term treatment of hypotension

Not recommend in septic shock : ↑lactate , ↓ renal clearance , ↓hepatosplanchic blood flow

Tachyphylaxis
Dose :
Bolus : 10-200 ug
Infusion : 0.05-2 ug/kg/min

Age has effect on the dose response > titrating dose

Dopamine



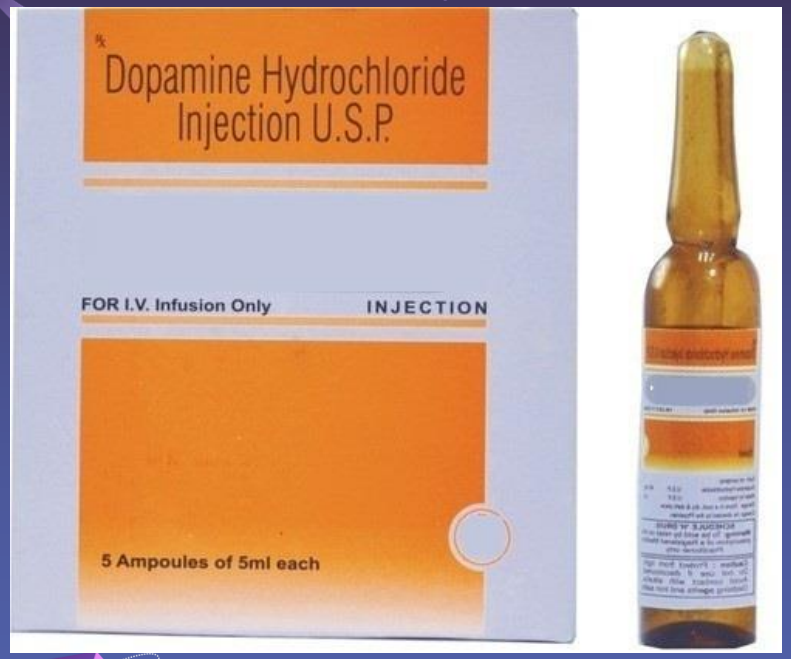
Endogenous catecholamine

Should only used for vasodilatory shock in highly selected populations with relative bradycardia

Agonism of “D1-type receptors”

Increase cardiac output
(inotropic and chronotropic effect)

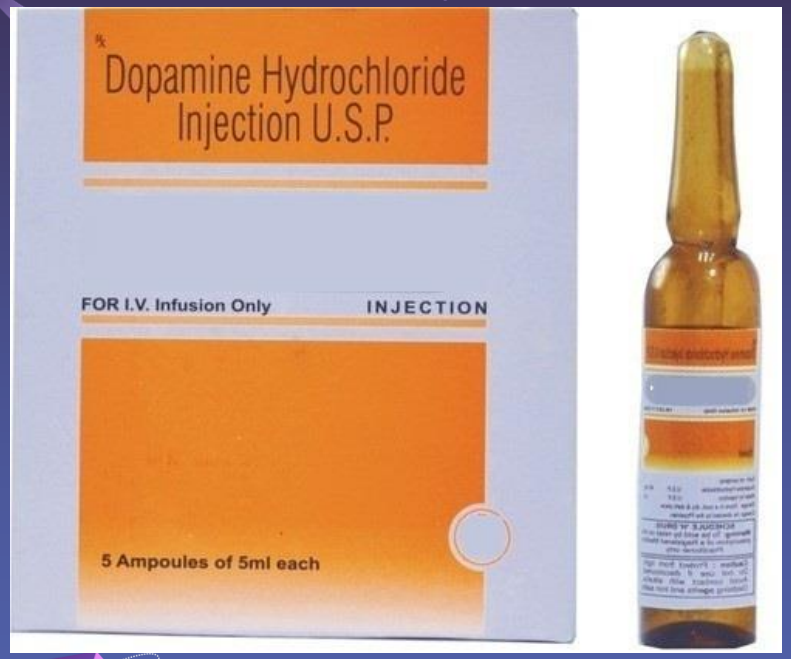
Dopamine



D1-type receptors (D1 and D5)
Direct arterial vasodilation

D2-type receptors (D2 , D3 , D4)
Increase smooth vascular tone

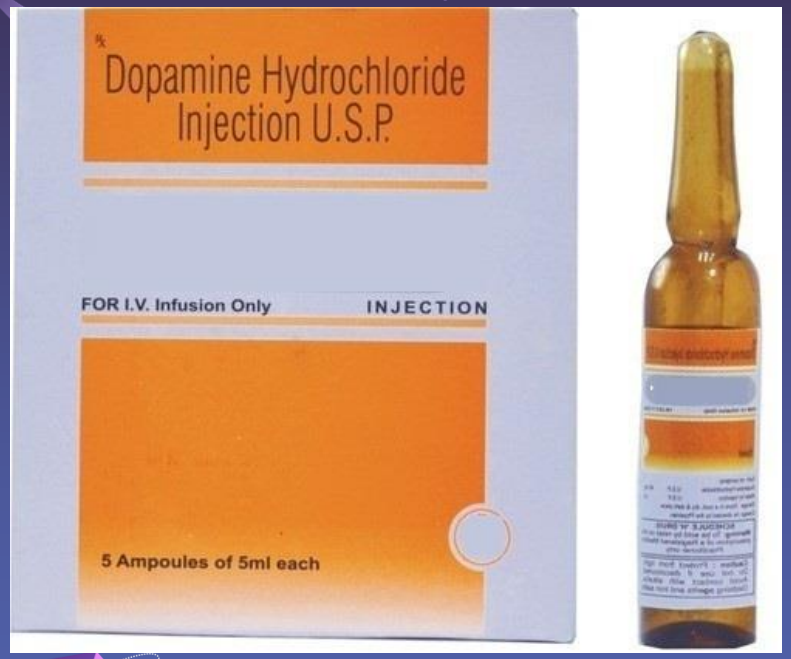
Dopamine



Dose dependent

0.5-2 ug/kg/min	2-10 ug/kg/min	>10 ug/kg/min
Low dose	**Intermediate dose**	**High dose**
D1-type receptors	β1 receptors >>> chronotropy , inotropy , lusitropy	α receptors >>> vasoconstriction

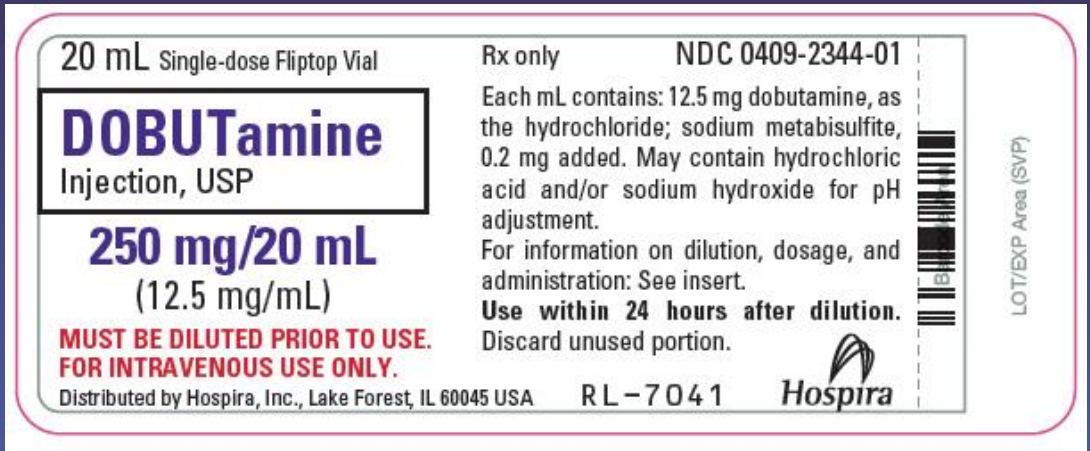
Dopamine



Not used for the routine management of vasodilatory shock

Useful in the subset of patients with impaired systolic heart function

Dobutamine



Synthetic catecholamine

Used for cardiogenic shock

Not be used in vasodilatory shock

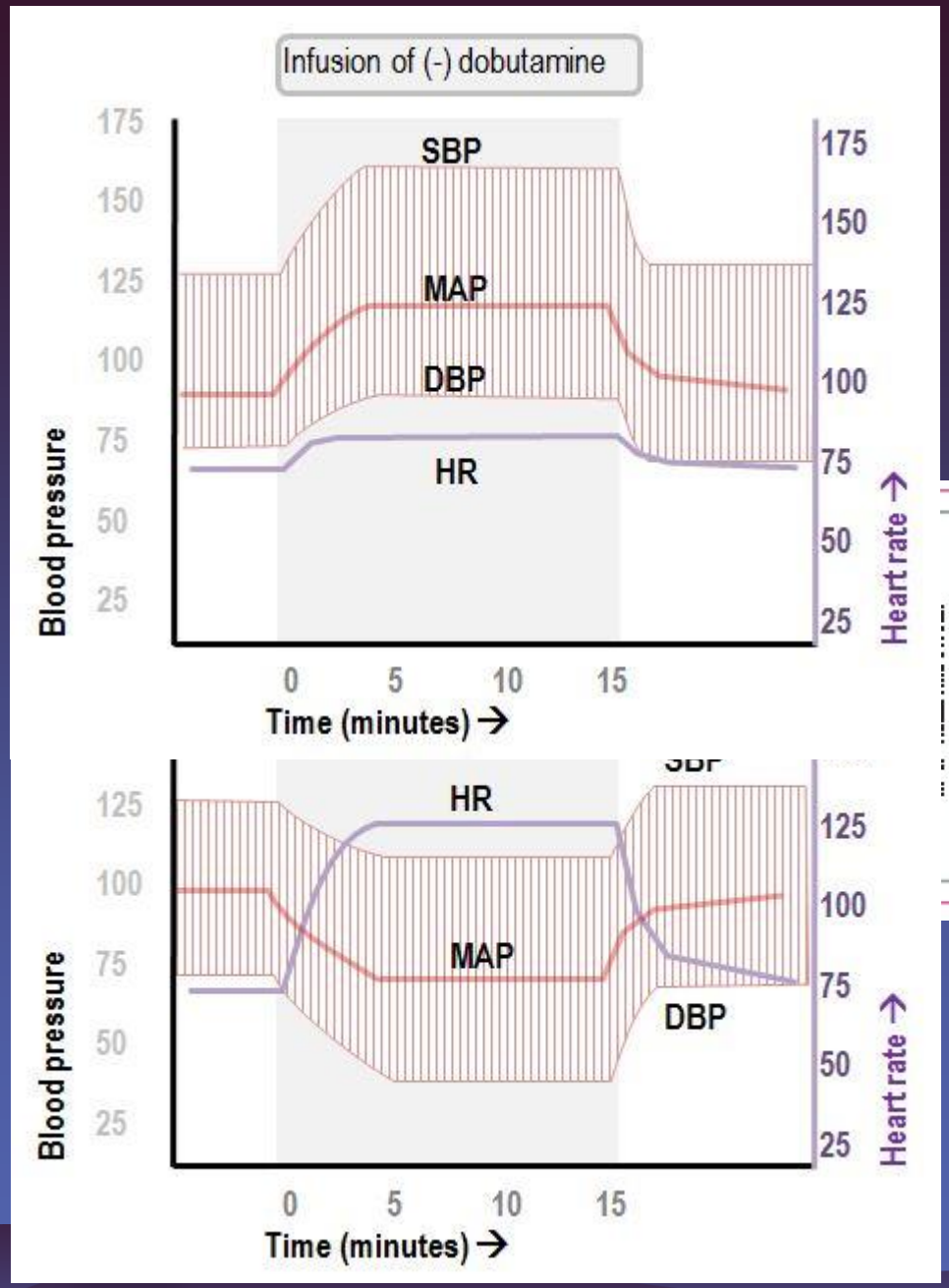
Dobutamine

Negative enantiomers

Predominate α1 receptors agonist
Weak β1,2 receptors agonist

Positive enantiomers

Predominate β1,2 receptors agonist
α1 receptors antagonist



Negative enantiomers

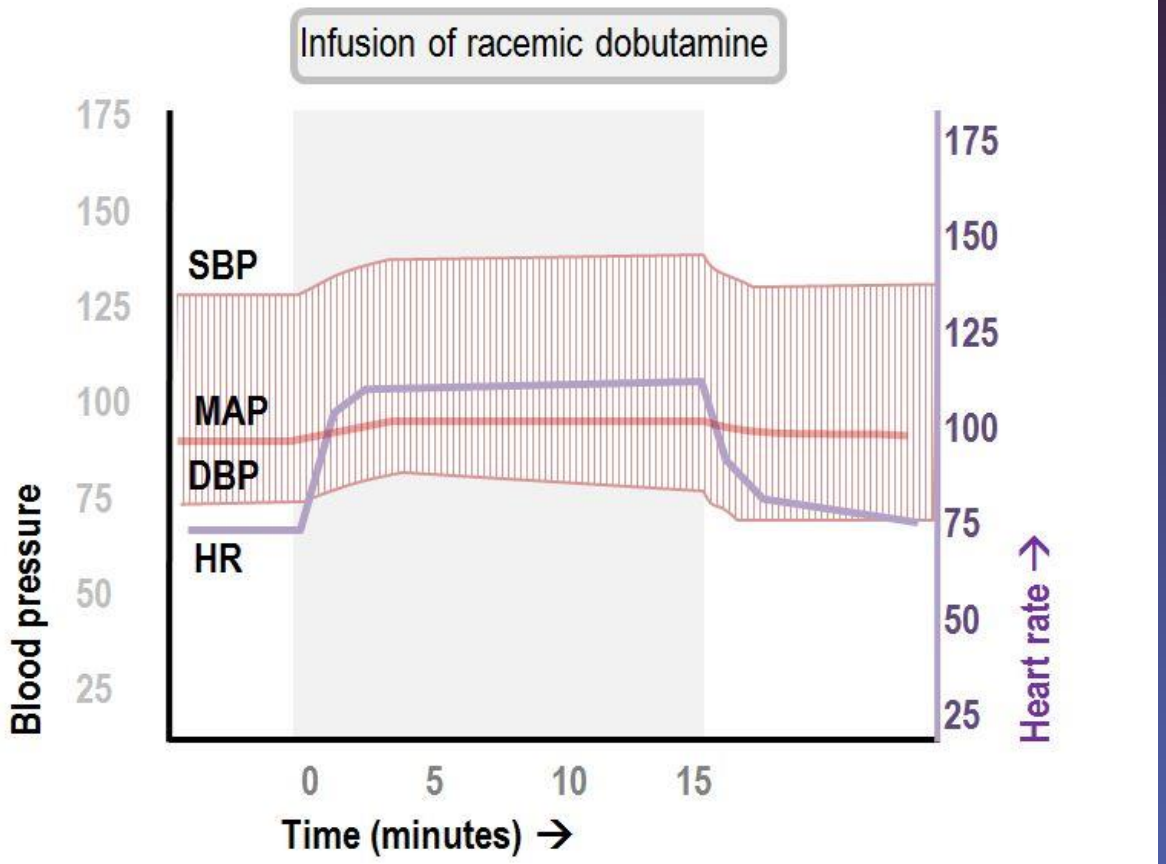
Predominate α1 receptors agonist
Weak β1,2 receptors agonist

Positive enantiomers

Predominate β1,2 receptors agonist
α1 receptors antagonist

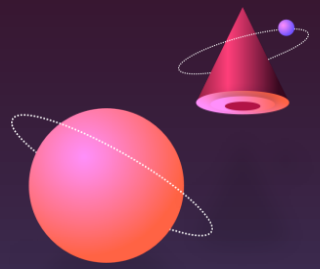
Dobutamine


20 mL Single-dose Fliptop Vial
Rx only
NDC 0409-2344-01
DOBUTamine
Injection, USP
250 mg/20 mL
(12.5 mg/mL)
MUST BE DILUTED PRIOR TO USE.
FOR INTRAVENOUS USE ONLY.
Each mL contains: 12.5 mg dobutamine, as the hydrochloride; sodium metabisulfite, 0.2 mg added. May contain hydrochloric acid and/or sodium hydroxide for pH adjustment.
For information on dilution, dosage, and administration: See insert.
Use within 24 hours after dilution.
Discard unused portion.
Distributed by Hospira, Inc., Lake Forest, IL 60045 USA
RL-7041
Hospira
LOT/EXP Area (SVP)


Infusion of racemic dobutamine
SBP
MAP
DBP
HR
Blood pressure
Heart rate →
Time (minutes) →
175
150
125
100
75
50
25
0
5
10
15

Rescue agents

Rescue agents



Corticosteroids

Methylene blue

Thiamine

Corticosteroids

1st line rescue agents

Cortisol 1st corticosteroid released by HPA axis

Sensitivity to Ang-2 ,NE , Epi : mediation of vasoconstriction

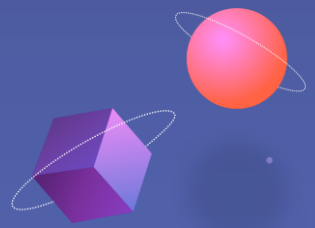
Decrease production of NO : mediation of vasodilation

Corticosteroids

Steroid in vasodilatory shock is safe

Increase rate hyperglycemia

Not result in increase rate of serious adverse events
(GI bleeding , superinfection)



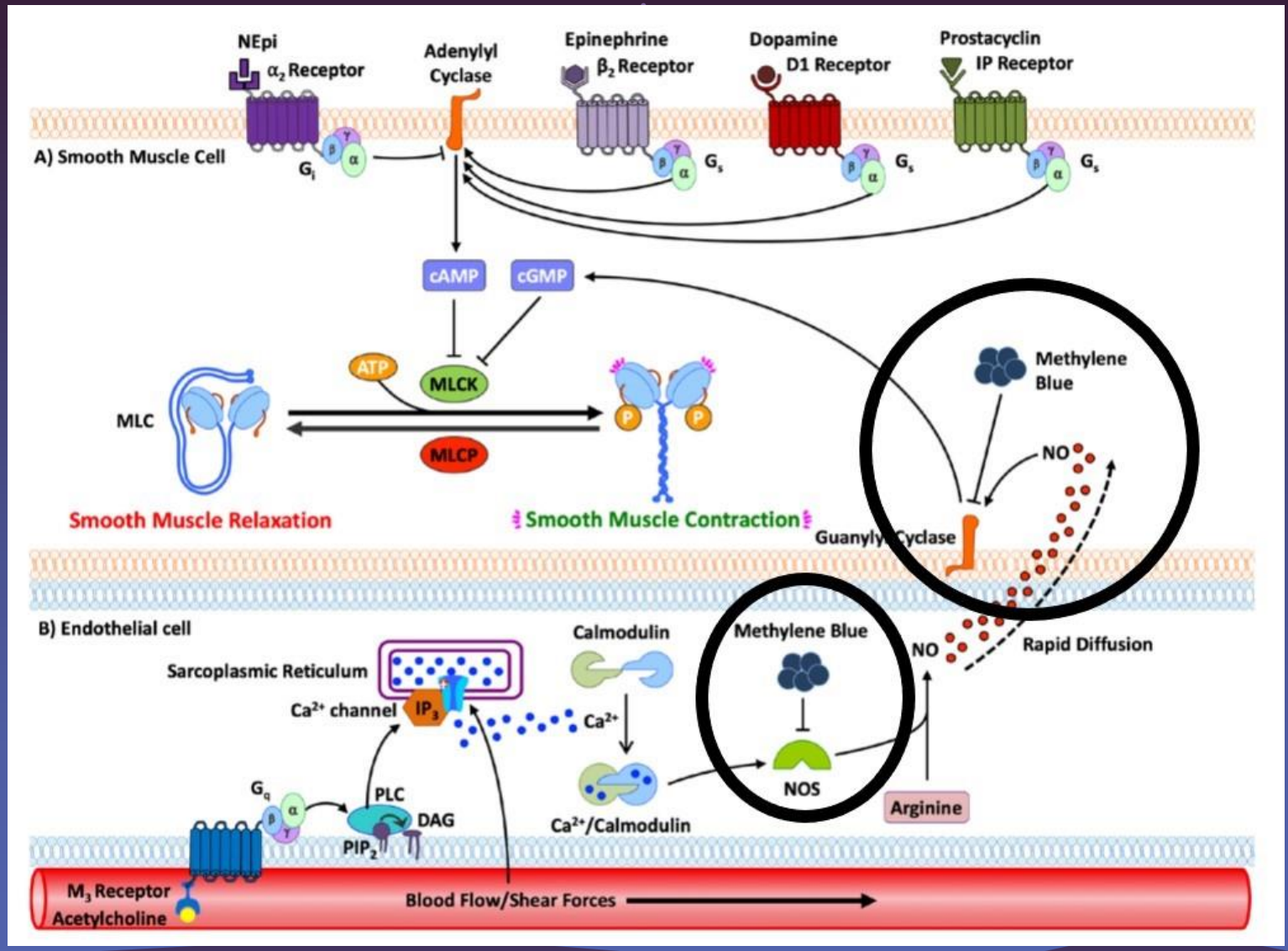
Methylene blue

Inhibits NOS and guanylyl cyclase

Preventing vasodilation
Increase MAP , SVR without HR

Utilizes mechanism distinct from vasopressor

Methylene blue



Methylene blue

Administered intravenous dose
1-2 mg/kg over 15 minutes

Followed infusion 0.5 mg/kg
over 6 hours

Thiamine

Vitamin B1 is an essential cofactor in the Krebs cycle

Deficiency interrupts the oxidative energy pathway

- increase anaerobic metabolism
- increase lactic acid production

Thiamine

Benefits in thiamine deficiency

High prevalence of thiamine deficiency in septic shock

Current finding suggest thiamine is unlikely to be universal

Emerging agents

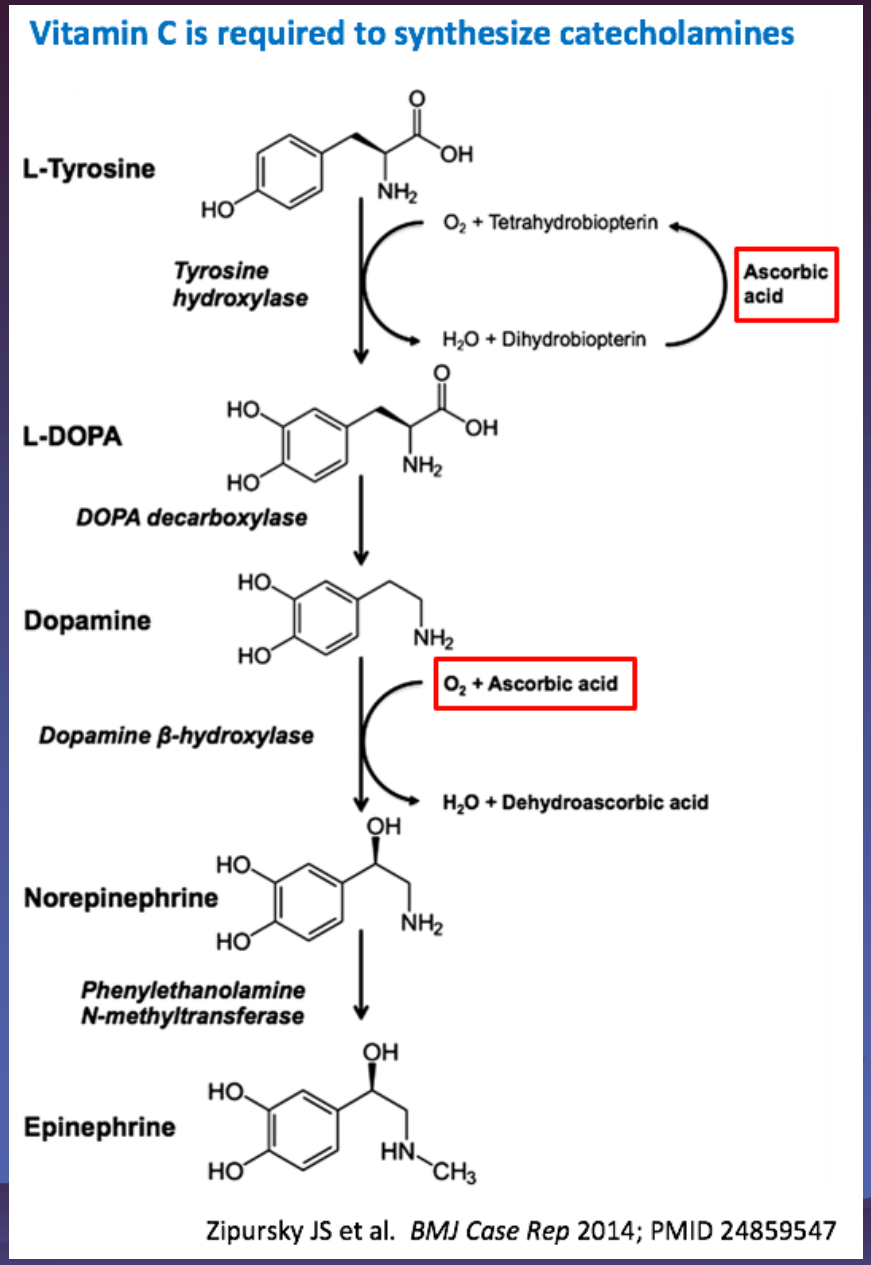
Ascorbic acid

Emerging therapeutic option for the treatment of septic shock

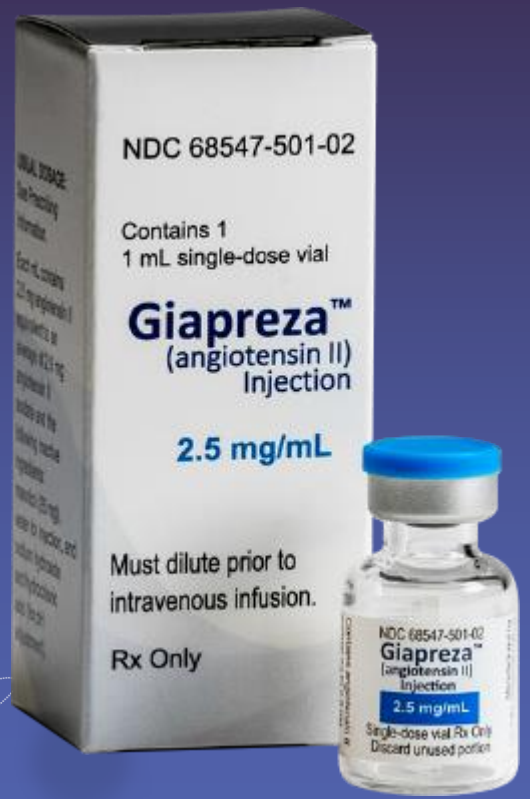
Cofactor in biochemical pathway for synthesis of catecholamine

Supplement in vasodilatory shock

Ascorbic acid



Angiotensin II



Natural hormone in RAA system

Activation of AT1 receptor

Smooth muscle contraction and stimulate release of ADH , aldosterone

Angiotensin II

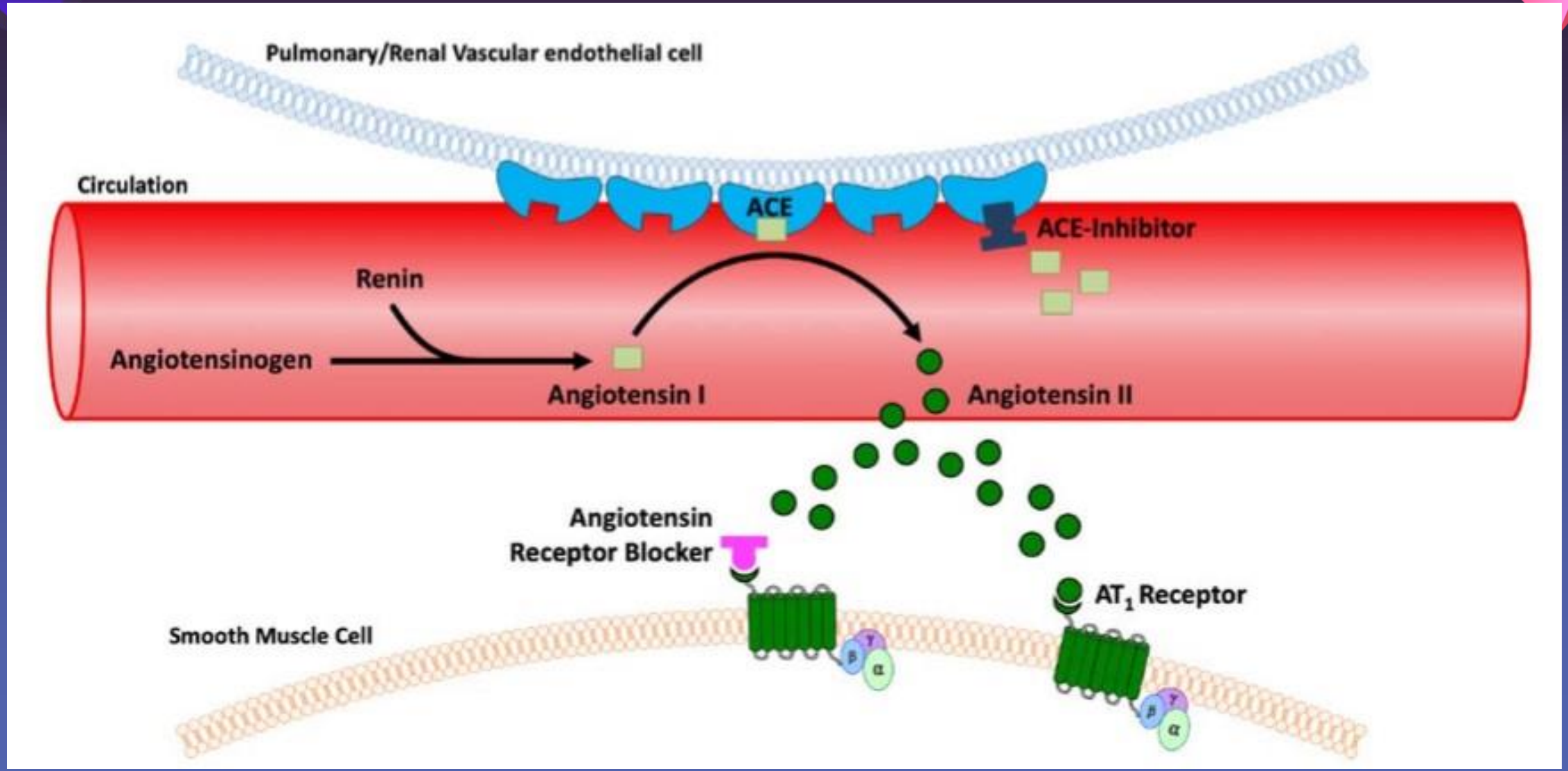
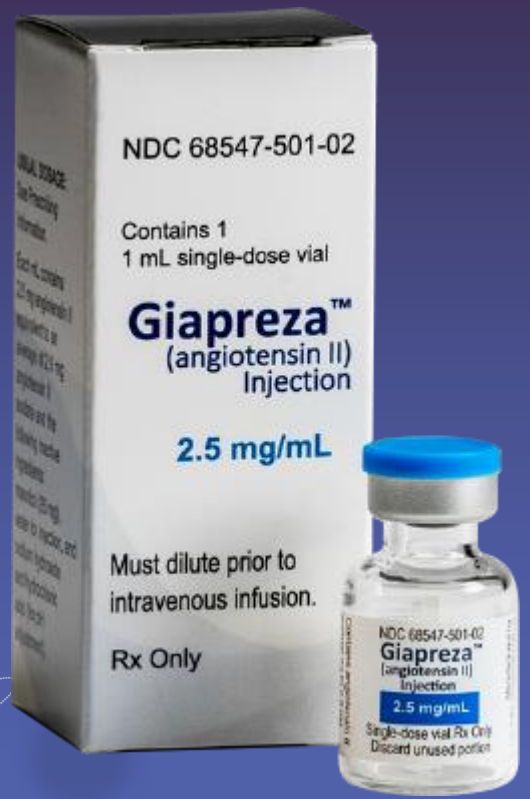


Table 2. Summary of Key Studies Investigating Angiotensin II

Reference	Design	Population	Dose Range	Outcome	*P* Value
Del Greco et al[116]	Case Series (n = 21)	Distributive, cardiogenic shock	0.23–100 μg min^{-1}	Return to normotension in 15/21 patients	N/A
Chawla et al[112]	RCT (n = 20)	Distributive shock	15–20 ng kg^{-1} min^{-1}	No difference in mean hour 1 NE dose. (7.4 ± 12.4 μg min^{-1} Ang-2 versus 27.6 ± 29.3 μg min^{-1} control)	.06
				No difference in mean hour 2 NE dose (7.3 ± 11.9 μg min^{-1} Ang-2 versus 28.6 ± 30.2 μg min^{-1} control)	.06
Khanna et al[117]	RCT (n = 344)	Distributive shock	20–40 ng kg^{-1} min^{-1}	Achieved target MAP by hour 1 (69.9% Ang-2 versus 23.4% SOC; OR = 7.95; 95% CI, 4.76–13.3)	<.001
				Decreased background NE-equivalent dose (−0.03 Ang-2 versus 0.03 SOC)	<.001
				No difference in 28-day all-cause mortality (46% versus 54%; HR = 0.78; 95% CI, 0.57–1.07)	.12
Wunderink et al[118]	Post hoc analysis (n = 141)	Distributive shock	Not reported	Increased 28-day mortality with Ang-2 depletion (HR = 1.78; 95% CI, 1.25–2.53)	.002
				Increased 28-day mortality with Ang-2 depletion and treatment with SOC vasopressors (HR = 1.77; 95% CI, 1.10–2.85)	.019
				Attenuation in mortality with Ang-2 depletion and treatment with Ang-2 (HR = 0.64; 95% CI, 0.41–1.00)	.047
Szerlip et al[119]	Post hoc analysis (n = 225)	Distributive shock, subset with APACHE-II score >30	Not reported	Decreased 28-day mortality in subset with APACHE-II score >30 (51.8% Ang-2 versus 70.8% SOC; HR = 0.62; 95% CI, 0.39–0.98)	.037
Tumlin et al[120]	Post hoc analysis (n = 105)	Distributive shock, subset with AKI requiring RRT	15–20 ng kg^{-1} min^{-1}	Improved 28-day survival in subset with AKI requiring RRT (53% Ang-2 versus 30% SOC; HR = 0.52; 95% CI, 0.30–0.87)	.012
				Increased rate of liberation from RRT by day 7 (38% Ang-2 versus 15% SOC; adjusted HR = 2.90; 95% CI, 1.29–6.52)	.007

Angiotensin II



Ang-2 deficient > high mortality

ACE deficiency cause of Ang-2 depletion

Ang-2 supplementation in Ang-2 deficiency ↓mortality

Patient with pulmonary pathology may also benefit from Ang-2 administration

CONCLUSION

- **Different mechanism of vasoconstrictors for treating vasodilatory shock**
- **Medications target :**
  - RAA system (Ang-2)
  - symptathetic nervous system
  - Vasopressin system
- Thiamine , ascorbic acid important in biochemical pathways
- **Emerged agents**
  Angiotensin II , ascorbic acid

Table 1. Receptor Distribution and Pharmacologic Effects on Heart, Vasculature, and Kidneys

Action	Receptor	Drug
Heart		
Chronotropy	β_1- and D1-type receptors	Epinephrine, dopamine
Inotropy and lusitropy	β_1- and D1-type receptors	Epinephrine, dopamine
Coronary blood flow	D1-type receptors and increased CBF related to increased inotropy	Dopamine
Peripheral arteries		
Vasodilation	β_2-, AT_2-, D1-type receptors	Epi (low dose), dopamine (low dose)
Vasoconstriction	α_1-, α_2-, V_1-, AT_1-, D2-type receptors	NE, phenylephrine, vasopressin, terlipressin, Ang-2, Epi (high dose), dopamine (high dose)
Kidneys		
Increased renal blood flow, naturesis, diuresis	D1-type receptors	Dopamine
Reduced aldosterone secretion	D2-type receptors in adrenal gland	Dopamine
Increased aldosterone secretion	AT_1 receptors	Ang-2
Free water retention	V_2, AT_1 receptors	Vasopressin, terlipressin, Ang-2

Thanks !