Regulation of Hemoglobin

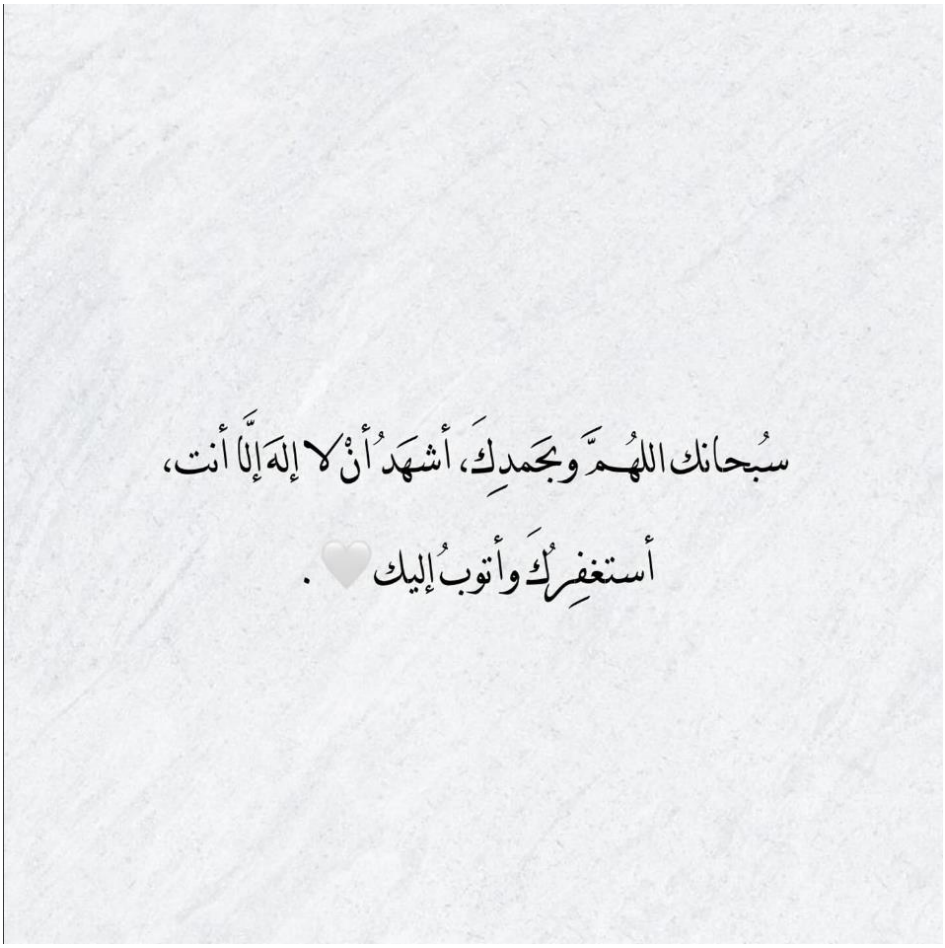
Effector / modulator	Type/Effect in case of the increase	How it interacts	Main molecular effect	T/R-state effect	O_2 affinity	P50	O_2 / physiological effect
O_2	Homotropic; positive allosteric effector	Binds heme; the ligand itself	Binding promotes conformational change that makes subsequent O_2 binding easier	Favors R-state	↑ Affinity	↓ P50	Promotes O_2 loading in the lungs; cooperative binding
H^+	Heterotropic; negative allosteric effector	Protonates key residues, especially β-chain His146	-Protonated His146 forms electrostatic interactions with Asp and Lys of the opposite α-chain -If unprotonated the salt bridges won't form , which satblizes R state	Stabilizes (low affinty) T-state	↓ Affinity	↑ P50	↑ O_2 release in metabolically active tissues tissues which are ,more acidic due to high metabolic rate; **Bohr effect**
CO_2	Heterotropic; negative allosteric effector	1) Indirectly via formation of H^+; 2) directly at free amino terminal groups → carbamates 3)Small fraction dissolved	-H^+ promotes electrostatic interactions; - carbamates add negatively charged groups that stabilize T-state	Stabilizes T-state	↓ Affinity	↑ P50	Facilitates O_2 unloading in tissues. About 75% of CO_2 effect is via H^+ and ~25% via carbamates
2,3-BPG	Heterotropic; negative allosteric effector	Binds in the central cavity of deoxyhemoglobin; **Ratio 1:1 with hemoglobin**	Forms salt bridges with terminal amino groups of plus , Lys and His143	Stabilizes T-state; binds deoxyhemoglobin preferentially	↓ Affinity	↑ P50	Facilitates O_2 release and decreases its upload rate. Increased at high altitude as adaptation
Cl^-	Heterotropic; negative allosteric effector	Interacts with N-terminus of α2 and Arg141 of α1	Electrostatic interactions stabilize the T-state	Stabilizes T-state	↓ Affinity	↑ P50	Facilitates O_2 release; contributes to chloride shift and charge balance
CO	Heterotropic; negative allosteric effector / **competitive inhibitor**	Competes with O_2 for heme binding	CO binding keeps affected heme in R-state; also increases the O_2 affinity of the remaining sites	Favors R-state at affected Hb	↑ affinity of remaining sites, while reducing available O_2-binding sites	The curve indicates high affinity but also low lvl of saturation due to the decline in binding sites	↓ O_2 unloading to peripheral tissues; CO poisoning can therefore cause tissue hypoxia

Comparison for better memorisation

What increases?	Affinity	P50	state	O_2 release	mechanism	in tissues
H^+ ↑ (pH ↓)	↓	↑	T-state	↑	Protonation →electrostatic interactions stabilize T	Active tissues → more H^+ → unload O_2
CO_2 ↑	↓	↑	T-state	↑	H^+ production + carbamate formation stabilize T + isohydric shift	Metabolism → CO_2 ↑ → unload O_2
2,3-BPG ↑	↓	↑	T-state	↑	Binds central cavity of deoxy-Hb and stabilizes T state	High altitude → 2,3-BPG ↑ → better O_2 delivery
Cl^- ↑	↓	↑	T-state	↑	Electrostatic interactions stabilize T	Works with chloride shift; helps unloading
Temperature ↑	↓	↑	Tendency toward T	↑	Directly lowers affinity	Exercise/fever → more O_2 needed → more unloading
O_2 ↑	↑	↓	R-state	↓ unloading / ↑ loading	Homotropic positive effector; binding makes additional O_2 binding easier	Lungs → load O_2
CO	↑ affinity of remaining sites	---	R-state at affected hemes	↓↓	Competes for heme + keeps bound sites in R state; keeping O_2 bound.	CO exposure → poor tissue unloading

**Hbf has a higher affinity than HbA because γ-chain has a serine instead of the polar lysine in the location143 which forms weaker interactions with 2,3-BPG resulting in an increase in affinity.

Quiz time……GOOB LUCK!!

https://forms.gle/cFF5joppJkFDzDYW8

All the info in this file is based on my understanding of Dr. Mamoun's lecture and slides.