

All Regulation - Mid

TCA cycle Regulation

FA synthesis

source of acetyl-CoA

Substrate availability

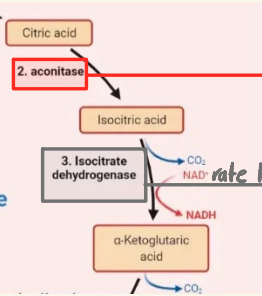
when their conc ↑↑
they promote enzyme activity

citrate synthase is inhibited by its own product → citrate^{-ve}

inhibits phosphofruktokinase (glycolysis)

ATP: allosteric inhibitor

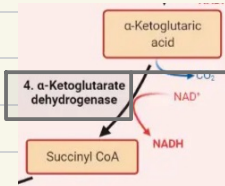
stimulate F1,6BPase → gluconeogenesis



Aconitase is inhibited by Fluoroacetate - rat poison - non competitive

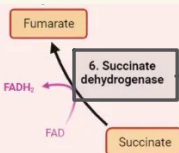
best regulation!!

+ ADP: low energy state, cell needs more energy → Activation of TCA
+ Ca⁺⁺: muscle cell in state of contraction → needs energy
NADH, ATP: indicates high energy state → inhibit TCA



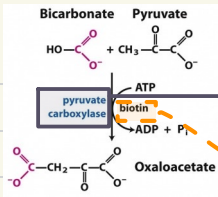
⊖ NADH, Succinyl CoA, GTP, Arsenite (non physiological non competitive)

⊕ Ca⁺⁺



⊖ inhibited by Malonate (competitive inhibition)

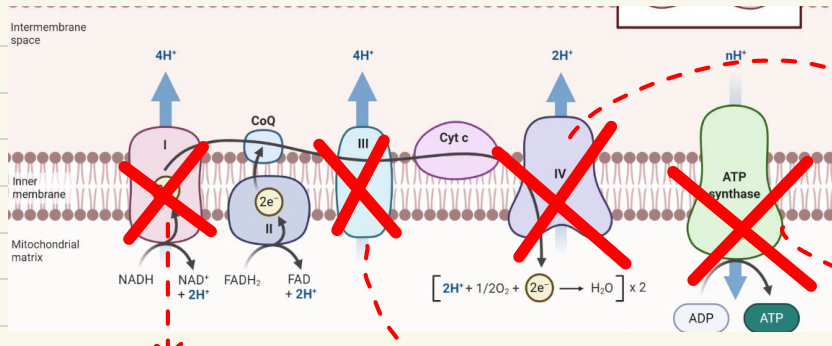
used as a pretreatment to reduce size of infarcts after heart attack



Pyruvate carboxylase **Activated by Acetyl CoA**
 requires **biotin**

why? A need for more oxaloacetate to "Pair" with acetyl CoA to keep TCA cycle running

→ **ETC inhibitors** - to verify correct arrangement of ETC components



CN^- , CO
 $\text{N} \equiv \text{N}^+ \equiv \text{N}^-$
 Complex IV - as
 oligomycin
 complex IV

Rotenone - complex I

Antimycin - complex III b

Inhibitor	Target Complex/Component	Mechanism of Action	Effect on ETC
Rotenone, Amytal	Complex I	Blocks electron transfer from NADH to Coenzyme Q (ubiquinone)	Stops the NADH pathway, but the FADH_2 pathway (via Complex II) remains functional.
Antimycin A	Complex III	Blocks electron transfer from cytochrome b to cytochrome c	Prevents both NADH and FADH_2 pathways, stopping electron flow past Complex III.
Cyanide, Azide, and Carbon Monoxide	Complex IV	Inhibit cytochrome a_3 , preventing oxygen reduction	Completely halts the ETC by blocking oxygen as the final electron acceptor, stopping all electron flow.
Oligomycin	Complex V	Inhibits ATP synthase, preventing proton flow through the enzyme	Halts ATP synthesis by preventing proton gradient utilization, indirectly slowing the ETC.

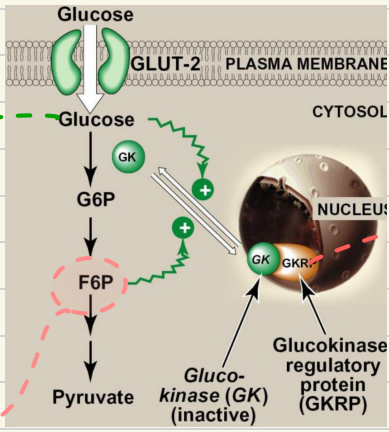
ser's help

Note:
 Some inhibitors can be used for cancer treatment
 }
 cyanoglycosides such as amygladin (misonomer B17)

in Oxidative phosphorylation → Most important factor in determining rate → ADP
 Respiratory control or acceptor control

Glycolysis regulation

Glucokinase regulation



When glucose conc $\uparrow\uparrow$
 it promotes dissociation of glucokinase from its regulatory protein

When F6P $\uparrow\uparrow$
 it signals the need to down regulate glycolysis by promoting sequestering of glucokinase into nucleus

when glucokinase is inactive it is sequestered in nucleus bound to glucokinase regulatory proteins (GKRP)

cytoplasm

Allosteric regulation of PFK-1 - regulation of step 3 of glycolysis

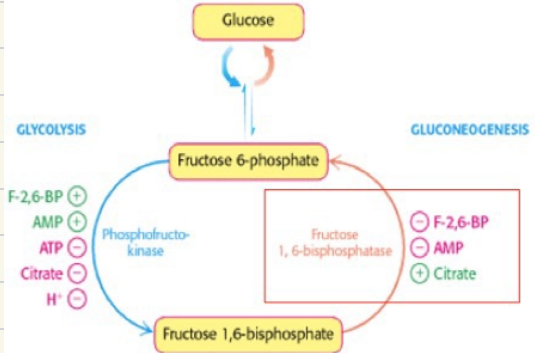
F-2,6-BP is a \oplus regulatory molecule

AMP \oplus signals a low energy state

ATP \ominus \rightarrow high energy state, no need to break-down anymore glucose

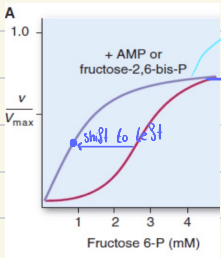
citrate \ominus \rightarrow product of TCA; reflects sufficient energy

H⁺ \ominus \rightarrow Active oxphos & high energy production



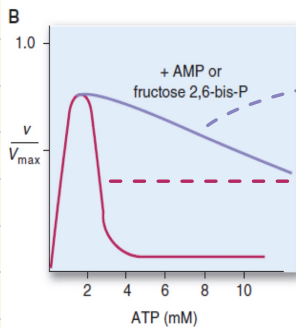
remember!!! it requires energy

Regulation of PFK₁ by F-2,6BP & AMP



it nearly reaches hyperbolic; even at very low conc → Activators can increase velocity
 this indicates higher enzymatic activity → higher reaction velocity at lower conc of F6P
 V_{max} stays the same!! (it only depends on enzyme conc)

other substrates? conc of ATP against velocity



decrease of reaction velocity caused by ATP inhibition occurs more gradually

shape of the curve reflects dual role of ATP

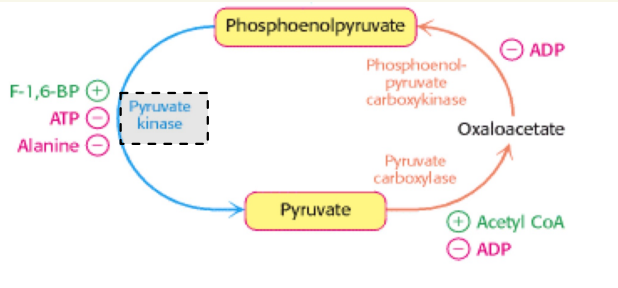
At low ATP conc. it acts as a substrate

ATP conc ↑↑ it functions as an allosteric inhibitor

Regulation of Pyruvate kinase

F-1,6-BP (+) →

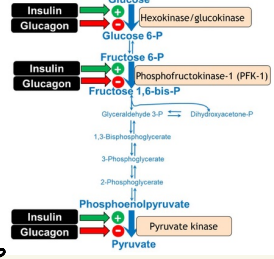
Feed back regulation
 it's produced in step 3 of glycolysis & act as a positive allosteric inhibitor



* ATP⁻ → signaling a high energy state

* Alanine⁻ : transamination of alanine → Pyruvate → Thus; ↑↑ alanine sufficient Pyruvate

Hormonal regulation of Phosphofruktokinase

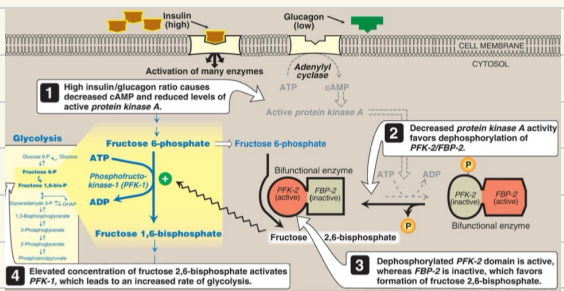


well-fed state

insulin levels $\uparrow\uparrow$

Activation of insulin receptors (receptor tyrosine kinase)

↓
 Kinase component of Bisfunctional enzyme (PFK-2/FBPase-2) is active, while phosphatase component is inactive



This leads to increased levels of (F-2,6-BP) an activator of (PFK-1) & inhibits gluconeogenesis

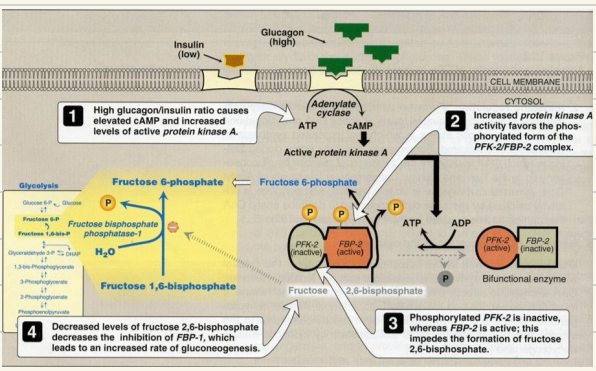
during fasting

Glucagon $\uparrow\uparrow$; glucagon binds to its GPCR which activates adenylate cyclase \rightarrow \uparrow cAMP

Activation of Protein kinase A

Phosphorylates bisfunctional enzyme

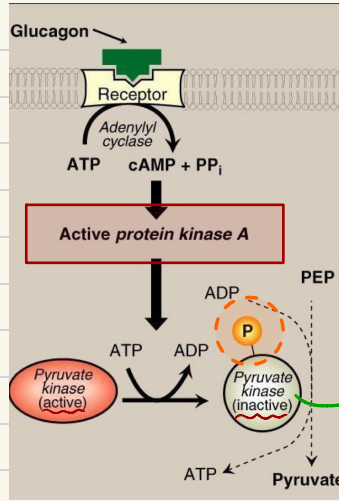
switches off kinase activity & activating phosphatase activity \rightarrow $\downarrow\downarrow$ F-2,6-BP \rightarrow inhibiting glycolysis & promote gluconeogenesis



Regulation of Pyruvate kinase

Active Protein kinase

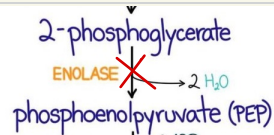
↓
inactivates Pyruvate kinase by phosphorylating it



Inorganic inhibitors of Glycolysis - non Physiologic

Fluoride → inhibits bacterial's Enolase

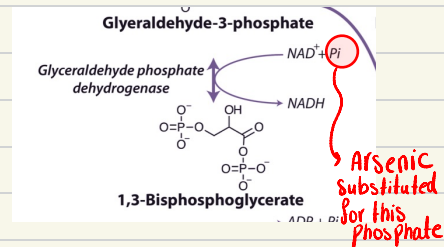
↳ prevention of dental caries



Arsenic Poisoning

→ Pentavalent Arsenic (Arsenate)

competes with phosphate as a substrate for GAPDH



Arsenate

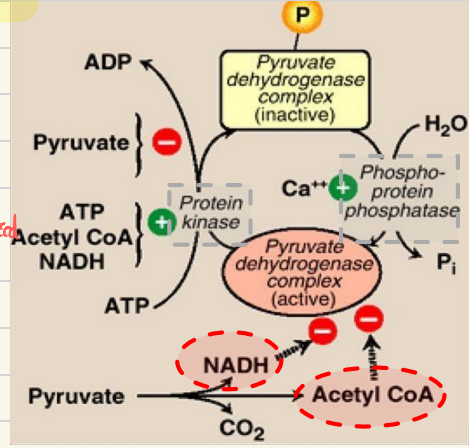
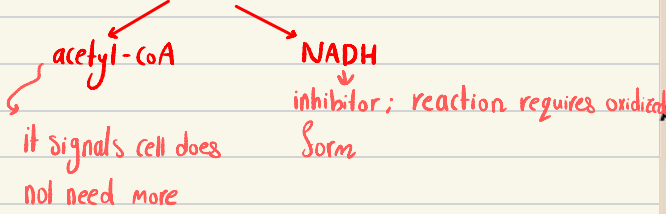
- * competes with P_i during glycolysis
- * ↓↓ ATP synthesis

Arsenite

inhibits Pyruvate dehydrogenase → stable complex with lipoic acid

Regulation of Pyruvate dehydrogenase complex

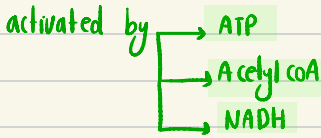
* Allosteric regulators - binds directly to PDH



* Two tightly bound regulatory enzymes

PDH Kinase

inactivates PDH by phosphorylation



inhibited by \rightarrow Pyruvate

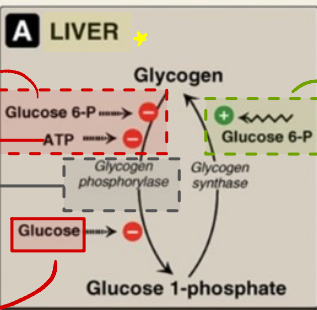
PDH Phosphatase

Activates PDH by dephosphorylation

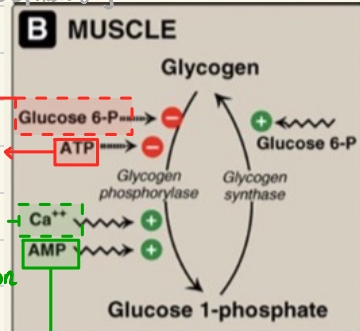
Activated by Ca^{2+}

Allosteric regulation of glycogen metabolism

note that glucose isn't a regulator in muscles; they lack (Glucose-6-Phosphatase)



allosteric activator in well-fed state

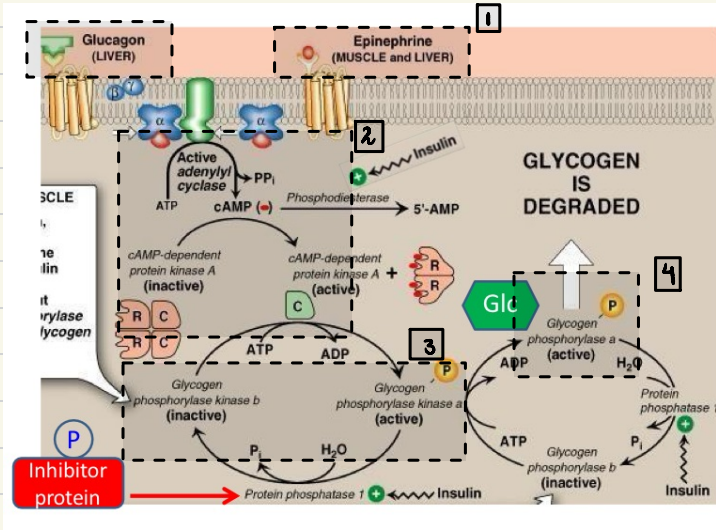


need of energy due to contraction

accumulates during muscle contraction \rightarrow indicates low energy

Hormonal regulation of Glycogen Metabolism

Glucagon & Epinephrine



1 Glucagon & Epinephrine they activate adenylyl cyclase by binding to GPCR

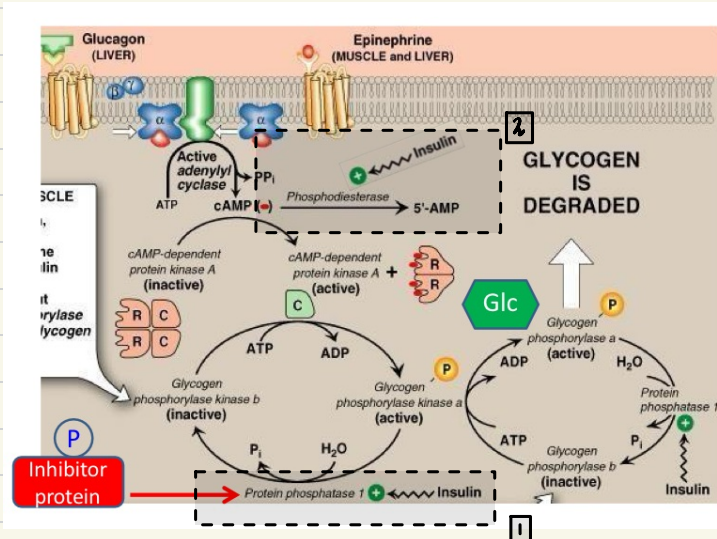
2 adenylyl cyclase makes cAMP activates Protein Kinase A & release catalytic subunit

3 Glycogen Phosphorylase Kinase activation by regulatory subunit

4 Activation of Glycogen Phosphorylase → starts Glycogen degradation

insulin

→ it does not bind to GPCR



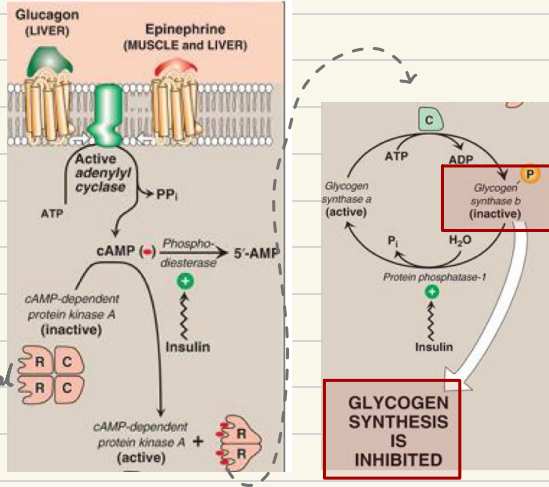
1 insulin activates Protein phosphatase-1 (PP1) inactivating both glycogen phosphorylase & glycogen Phosphorylase kinase

2 activating phosphodiesterase → changes cAMP to 5'-AMP turning off PKA

Regulation of Glycogen synthesis

* Glucagon & epinephrine inactivate glycogen synthase while insulin activates it to promote glycogen storage

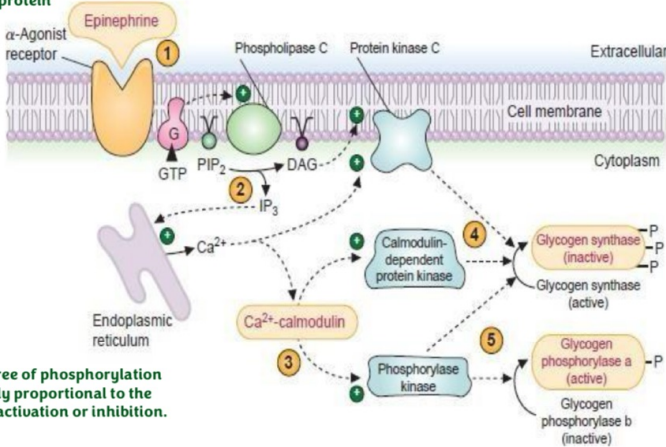
* Phosphorylation at different sites → inhibition is proportional to degree of phosphorylation



Epinephrine

Hormonal Regulation of Glycogen Metabolism

Notice: another pathway of G-protein



The degree of phosphorylation is directly proportional to the level of activation or inhibition.

1 Epi binds to an α -agonist activating a G-Protein

2 Signal cascade activation:

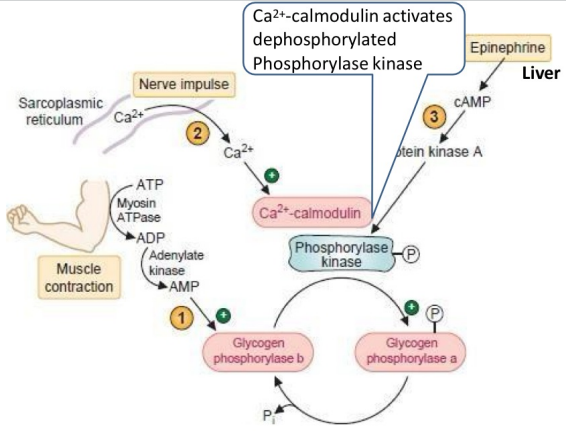
G-Protein activates phospholipase C
converts $PIP_2 \rightarrow IP_3$
 $PIP_2 \rightarrow DAG$

3 IP_3 exit mb & stimulates release of Ca^{++} at ER by binding to IP_3 gated channels

4 inactivation of glycogen synthase; Ca^{++} either activates PKC → inactivating glycogen synthase, or Ca^{++} binds to calmodulin making it active → activates calmodulin dependent PK → phosphorylates glycogen synthase → stopping glycogen synthesis

5 Activation of Glycogen Phosphorylase: Ca^{++} -calmodulin activates it → then phosphorylating glycogen phosphorylase → degrading glycogen

بَالِغٌ فِي حَسَنِ ظَنِّي بِاللَّهِ
فَإِنَّ هَذَا حَسَنُ الظَّنِّ أَنْ تَنَالَ
مَا ظَنَنْتُ. ♡



① Muscle contraction

ATP is used by myosine ATPase → ATP to ADP
Adenylate cyclase converts ADP to AMP →
activating muscle glycogen phosphorylase

② Nerve impulse :

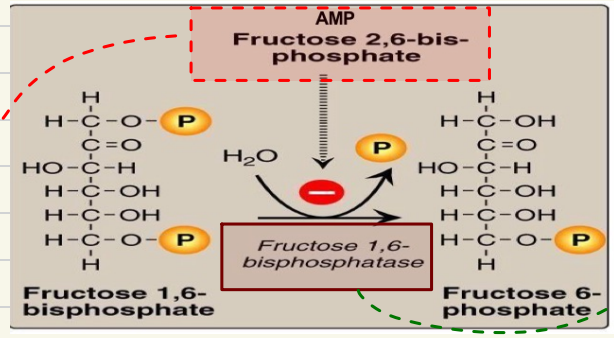
Triggers release of Ca^{++} from ER
it binds to calmodulin → forms Ca^{++} -calmodulin
which activates Phosphorylase kinase →
activates glycogen phosphorylase

③ liver response :

Epi → adenylyl cyclase → ↑ cAMP
PKA → phosphorylates phosphorylase kinase → glycogen breakdown

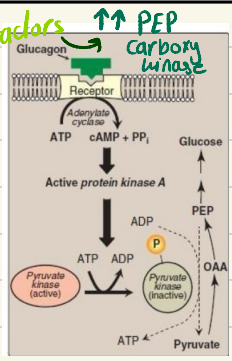
Regulation of gluconeogenesis

Notice that AMP &
Fructose 2,6-bisphosphate
inhibits F 1,6-BPase



⊕ Citrate
indicates active
Krebs cycle
so energy is
produced

can affect transcription factors
↑↑ Glucagon
↓ binds to GPCR
↓ activates adenylyl cyclase
↓ Produce cAMP
↓ activates PKA



PKA targets: *PKA phosphorylates bifunctional enzyme - same mechanism in page 5

* Pyruvate kinase : inhibits glycolysis

* glycogen synthase : Phosphorylated to stop glycogen synthesis

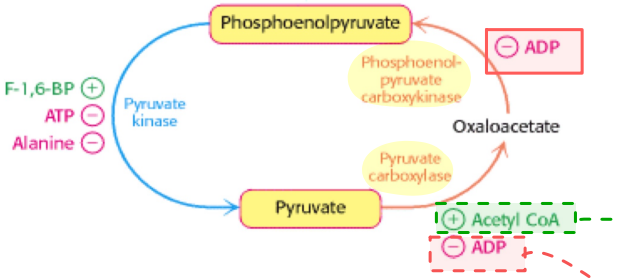
* Glycogen phosphorylase kinase : activated to increase glycogen

Regulation of gluconeogenesis - 2:6

* availability of Glucogenic substrates

* Synthesis of enzymes, increasing their conc & decreasing their degradation
↳ all affect gluconeogenesis & regulates it

Pyruvate carboxylase & PEP carboxykinase regulation



comes from degrading fatty acids
gluconeogenesis need energy

بدمولي: ♥♥

وأجعلني خيراً
لنفسي ولمن حولي
يا الله