AMPK

(AMP-ACTIVATED PROTEIN KINASE)

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AMPK – AMP-activated protein kinase

- present in all eukaryotic cells
- “sensor” of the cell energy status
- “switch” betwen anabolic and katabolic pathways
  - at the cell level
  - at the whole body level
- the sensed “battery” is the $\frac{\text{AMP}}{\text{ATP}}$ ratio

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$$\text{ATP} + \textit{coupled reaction reactants} \xrightarrow[\text{enzyme}]{\text{corresponding}}$$

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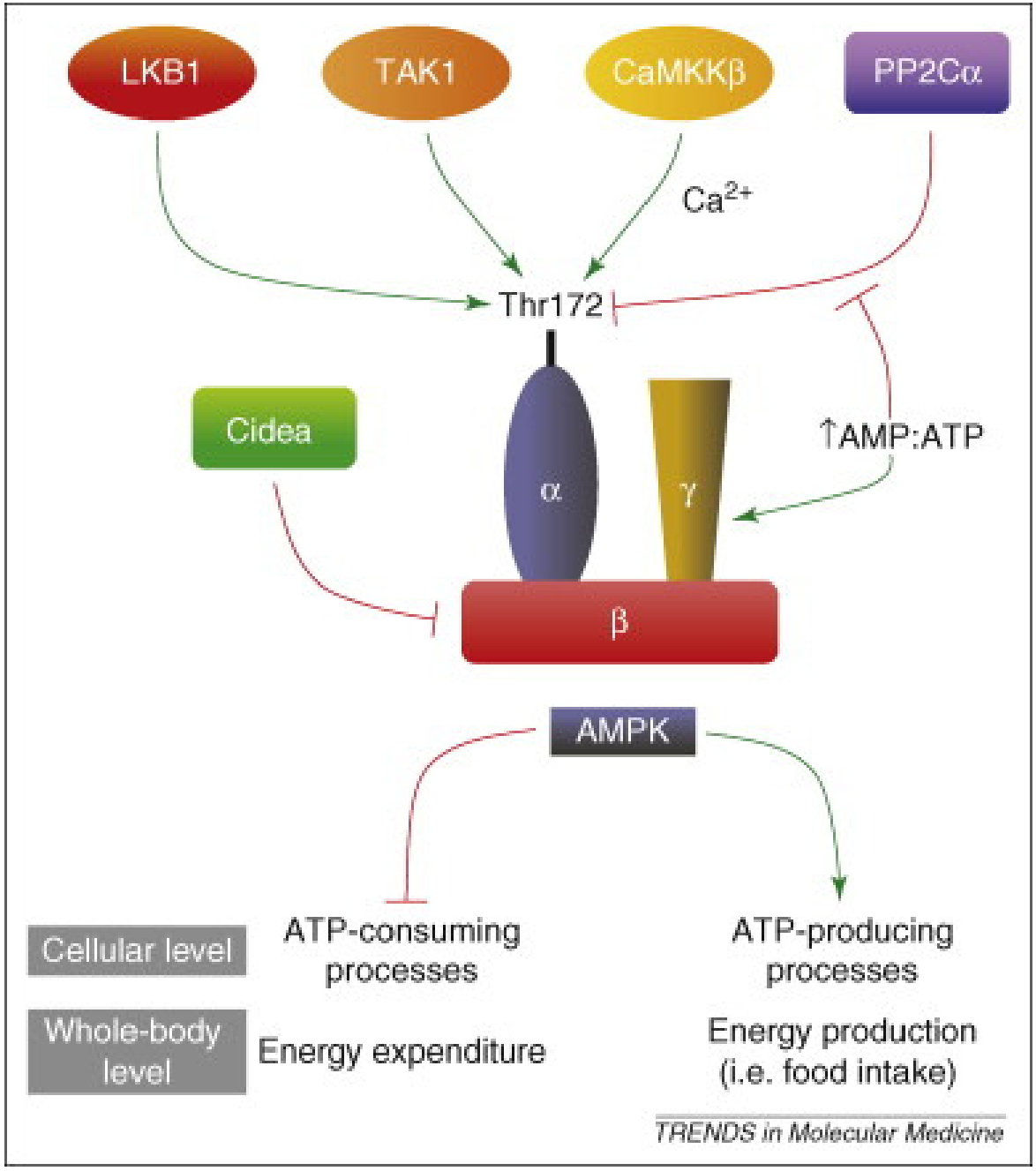
$$2\ \text{ADP} \overset{\text{adenylate kinase}}{\rightleftharpoons} \text{AMP} + \text{ATP}$$

AMPK STRUCTURE AND REGULATION



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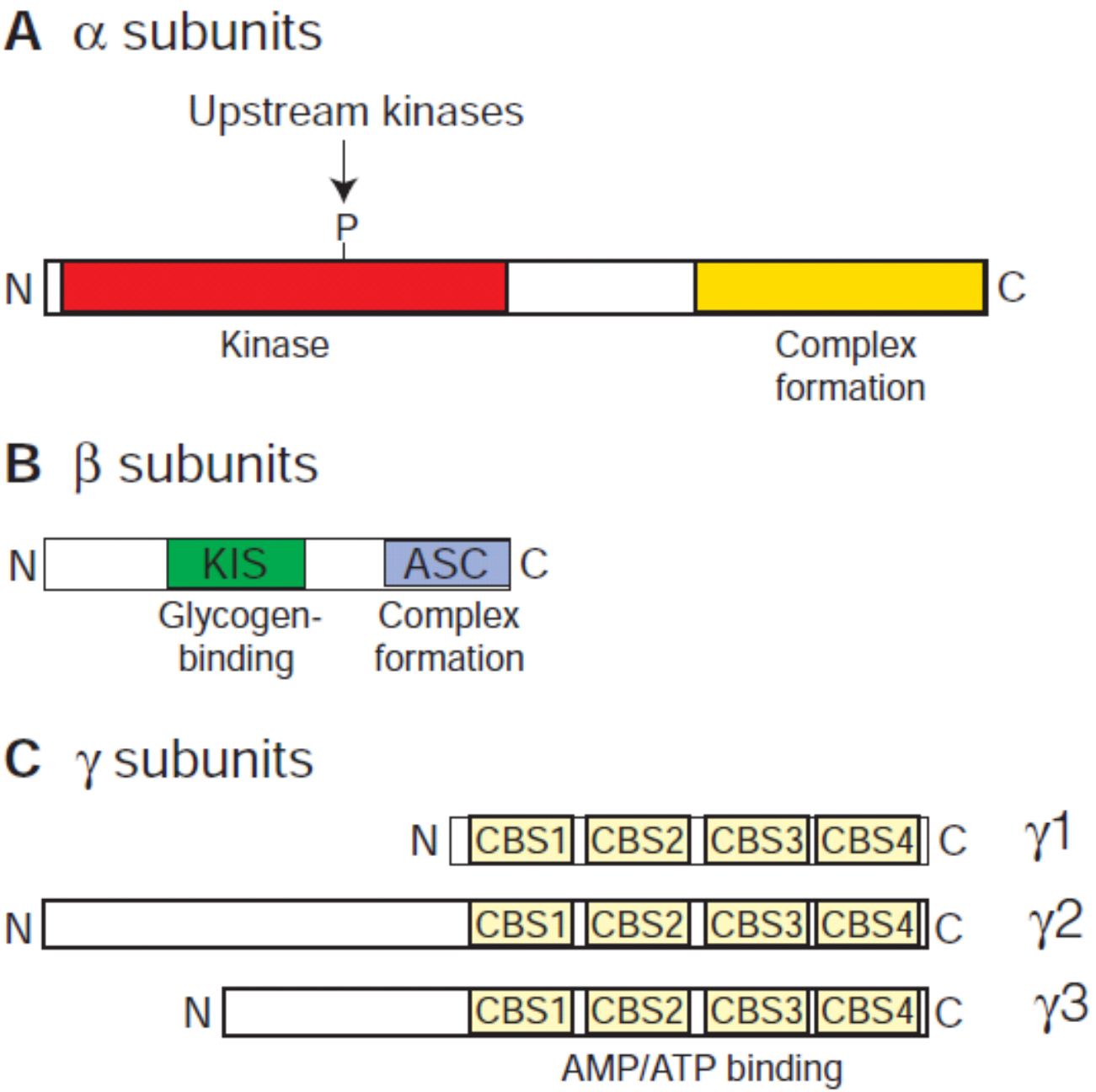
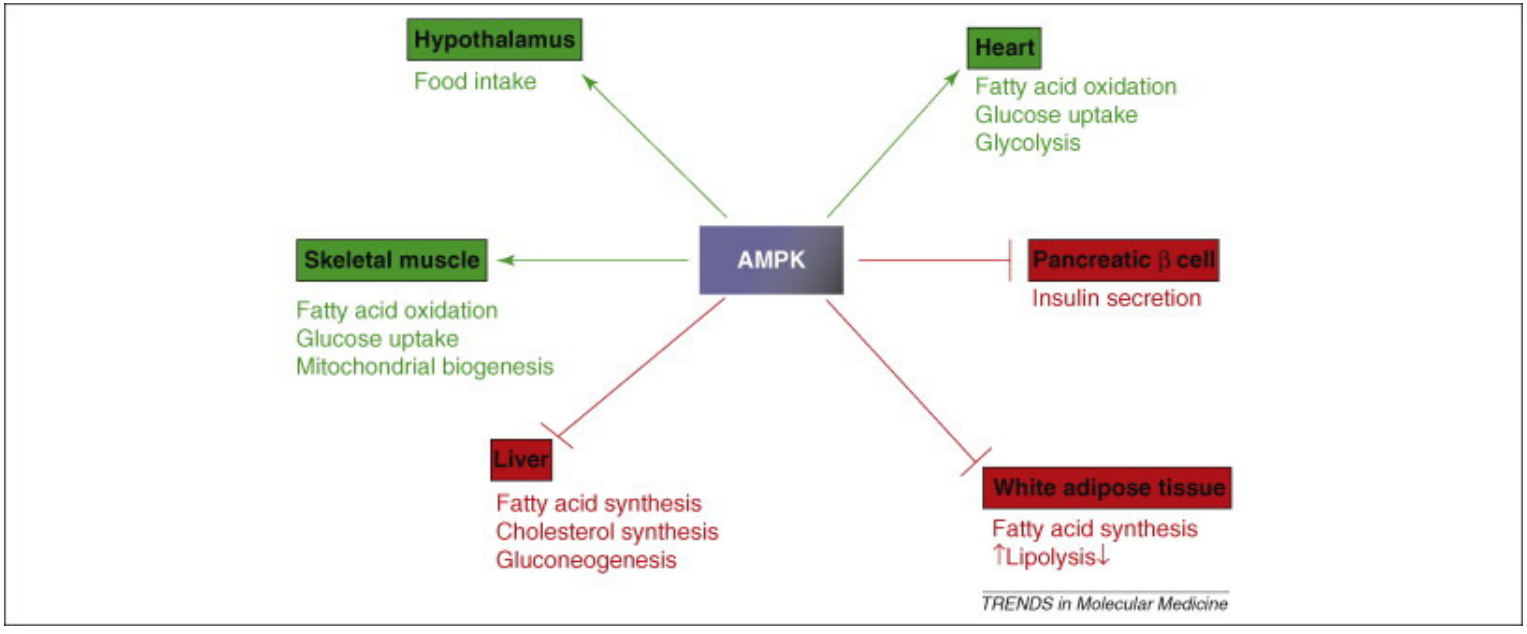


AMPK INFLUENCED PROCESSES

- anabolic
  - gluconeogenesis, synthesis of FA, cholesterol, triglycerides
- catabolic
  - glycolysis, FA oxidation
- příjem glukosy, příjem potravy



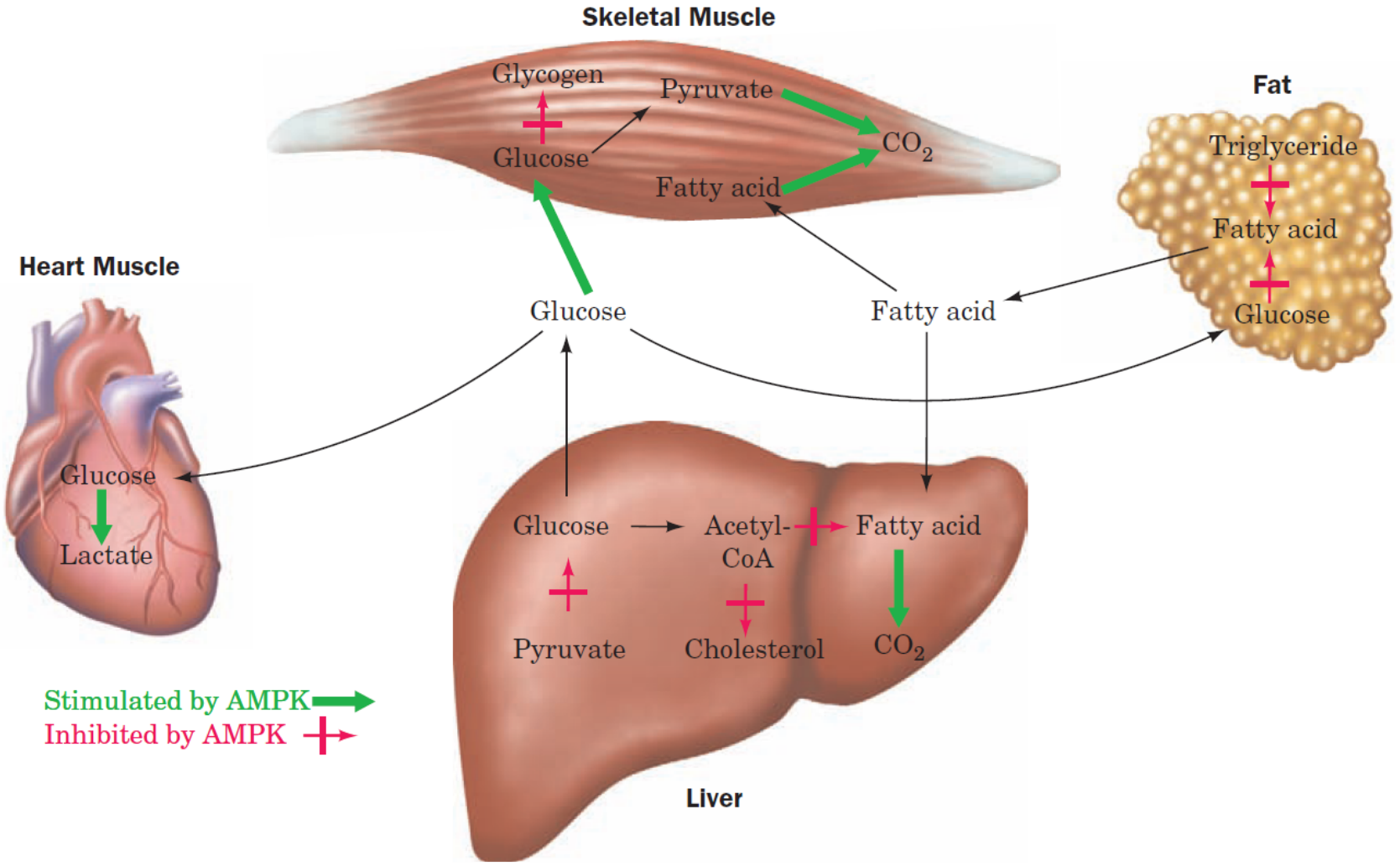
Lipid metabolism

- inhibition of ACC and HMG-CoA reductase
- decrease in FAS expression
- MCD activation
  - FA synthesis inhibition
  - decrease in inhibition of CPT1 $\Rightarrow$ increase in β-oxidation
- HSL inhibition

Glucose homeostasis

- equilibrium between hepatic Glc production and consumption in other tissues
- GLUT4 translocation and expression
- increase in hexokinase expression
- PEPCK and G6Pase inhibition
- GS inhibition
- high glycogen concentration suppresses AMPK activation

AMPK IN ORGANS



Hormone effect mediation

- leptin – food intake and neuroendocrine control of the energetic metabolism
  - quick AMPK activation by direct action on the muscle
  - slower activation via hypothalamus (α-adrenergic receptors) and melanocortin in the muscle
  - fiber type dependence
  - AMPK$\alpha 2\beta 1$ – phosphorylation of ACC-2 in cytoplasm
  - AMPK$\alpha 2\beta 2$ – translocation to the nucleus – PPARα expression induction

Hormone effect mediation

- adiponectin – activates Glc uptake and FA oxidation in the muscle, decreases Glc production in the liver and generally increases insulin sensitivity
  - lower concentration in obesity and type 2 diabetes
  - AMPK phosphorylation stimulation in liver, muscle and white fat
- resistin – inhibits FA uptake and oxidation in the muscle, increases hepatic Glc production, inhibits adipocyte differentiation and increases insulin resistance
  - metabolic state dependence – decreased under nutrient deprivation, increased in obesity and insulin resistance
  - decreases AMPK activation in the liver

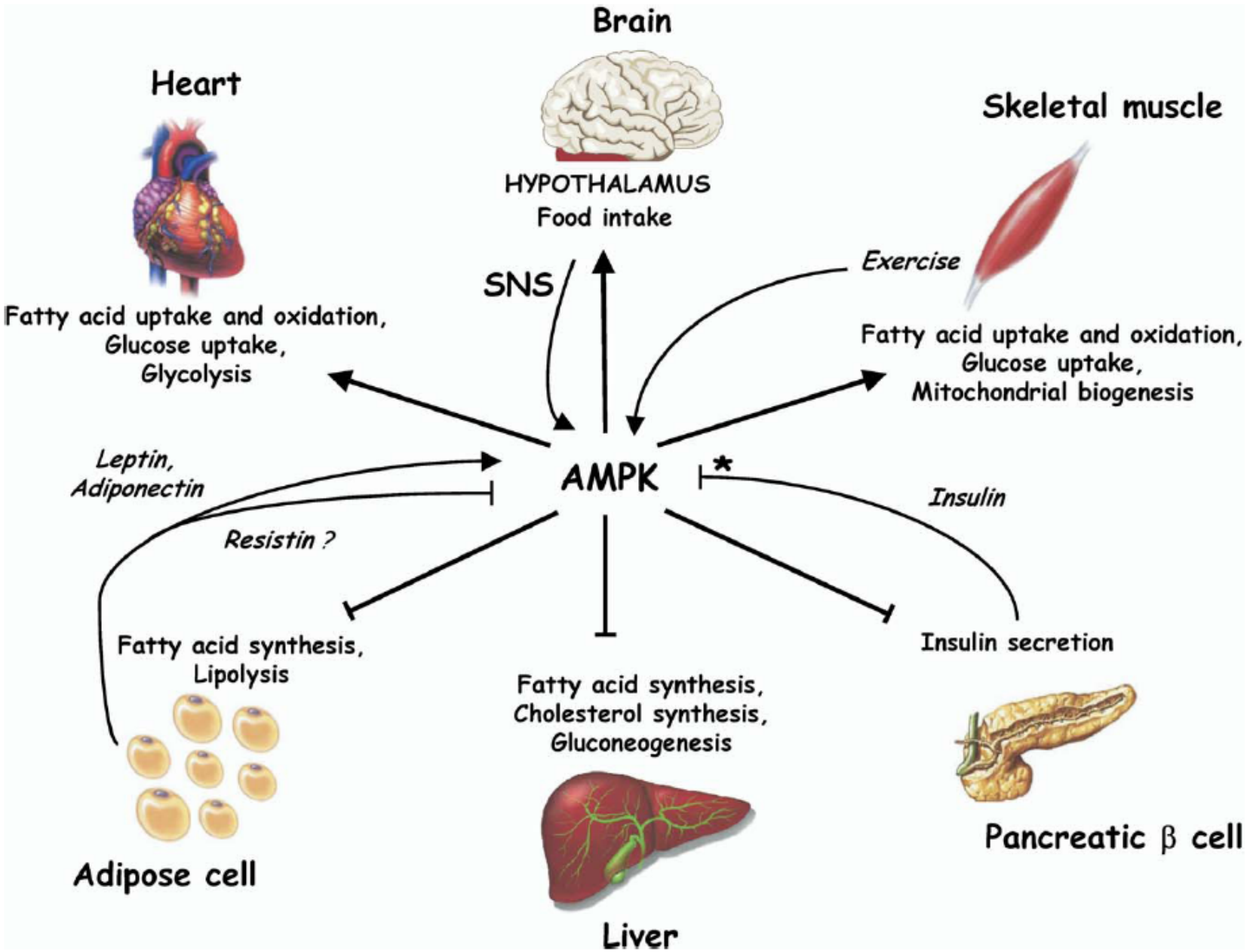
Hormone effect mediation

- ghrelin – produced mainly in the stomach
  - inhibits AMPK in the liver and white fat $\Rightarrow$ enhanced gluconeogenesis and lipogenesis
  - no influence on AMPK in the muscles
- endocannabinoids – stimulation of food intake, FA synthesis and gluconeogenesis in periferal tissues
  - inhibition of AMPK in the liver and white fat $\Rightarrow$ fat accumulation and weight gain
  - no influence on AMPK in the muscles

Hormone effect mediation

- thyroid hormones (T4 and T3)
  - tissue-specific influence on AMPK
  - – skeletal muscle – AMPK activation via CaMKKβ $\Rightarrow$ decrease in malonyl-CoA and FA oxidation stimulation
  - – AMPK deactivation in the liver
  - – food intake stimulation via AMPK activation in the hypothalamus

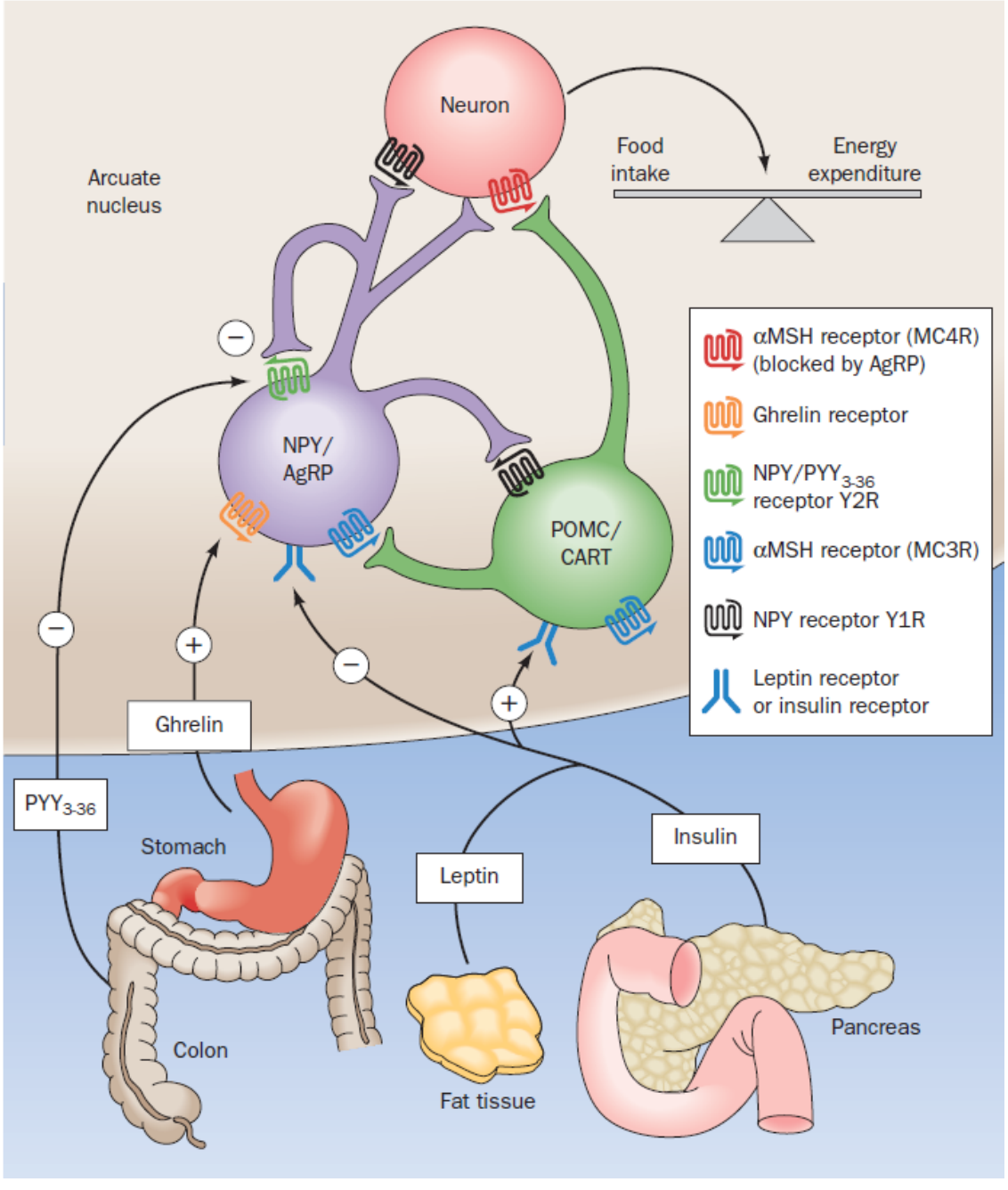
AMPK IN ORGANS



AMPK IN THE HYPOTHALAMUS

- fasting activates AMPK and feeding inhibits it
- AMPK activation enhances food intake and weight gain, AMPK inhibition decreases them
- hypothalamic FA metabolism modulator
  - ACC inhibition
  - FAS expresion decrease
  - $\Rightarrow$ decrease of the malonyl-CoA level $\Rightarrow$ CPT1 stimulate $\Rightarrow$
- anorectic signals (leptin, insulin, melanocortin...) – AMPK inhibition $\Rightarrow$ enhanced ACC activity
- orexigenic signals (glucocorticoids, cannabinoids, adiponectin, ghrelin...) – AMPK activation $\Rightarrow$ decreased ACC activity
- integration of hormonal and metabolic signals

Hypothalamic energy input control



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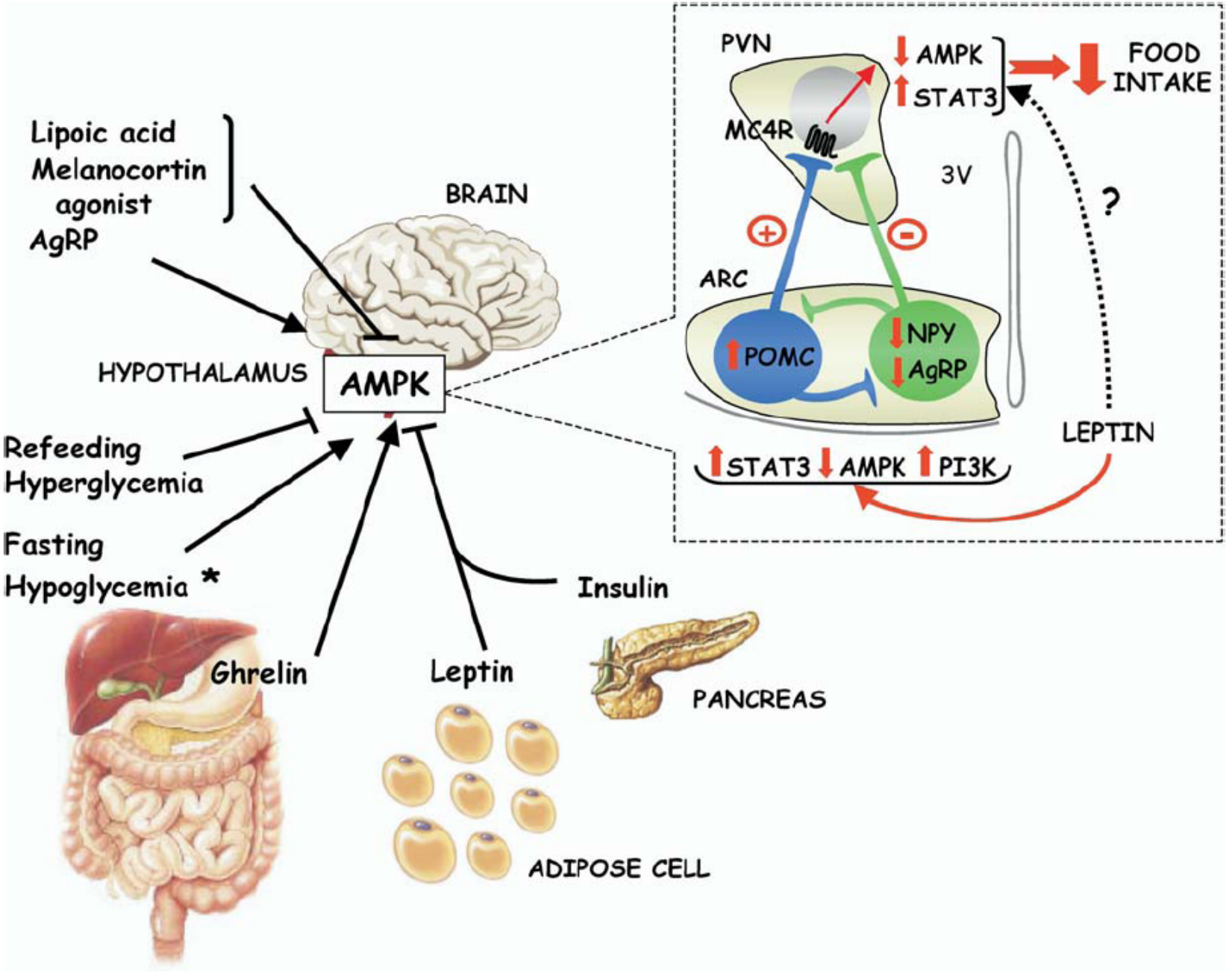
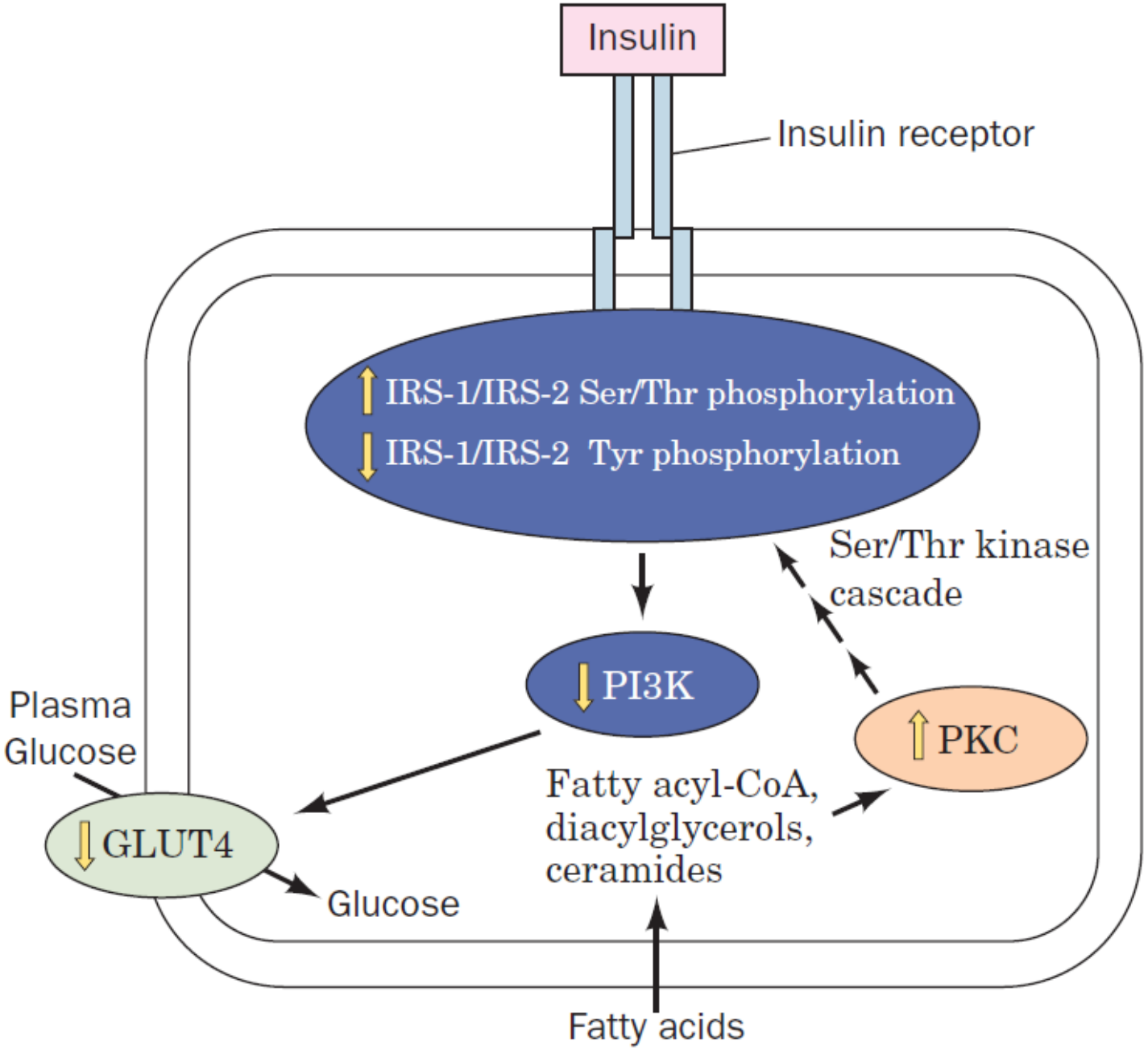
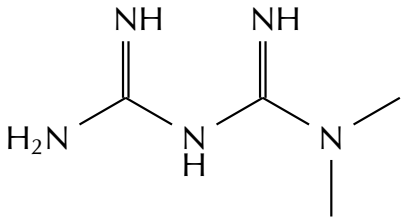


Fatty acids and insulin resistance

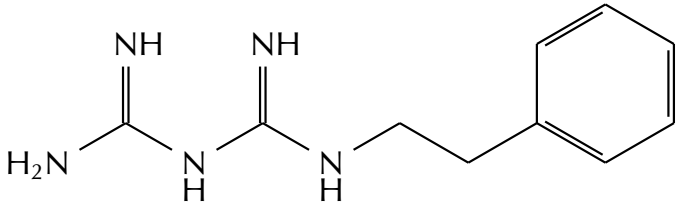


Antidiabetics

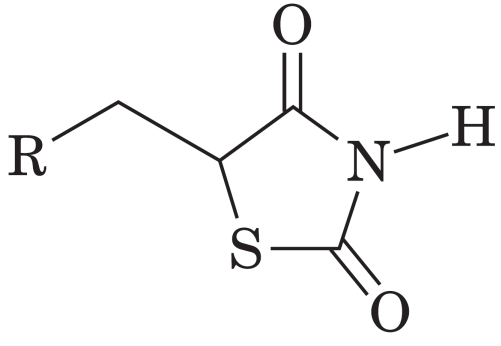
- metformin



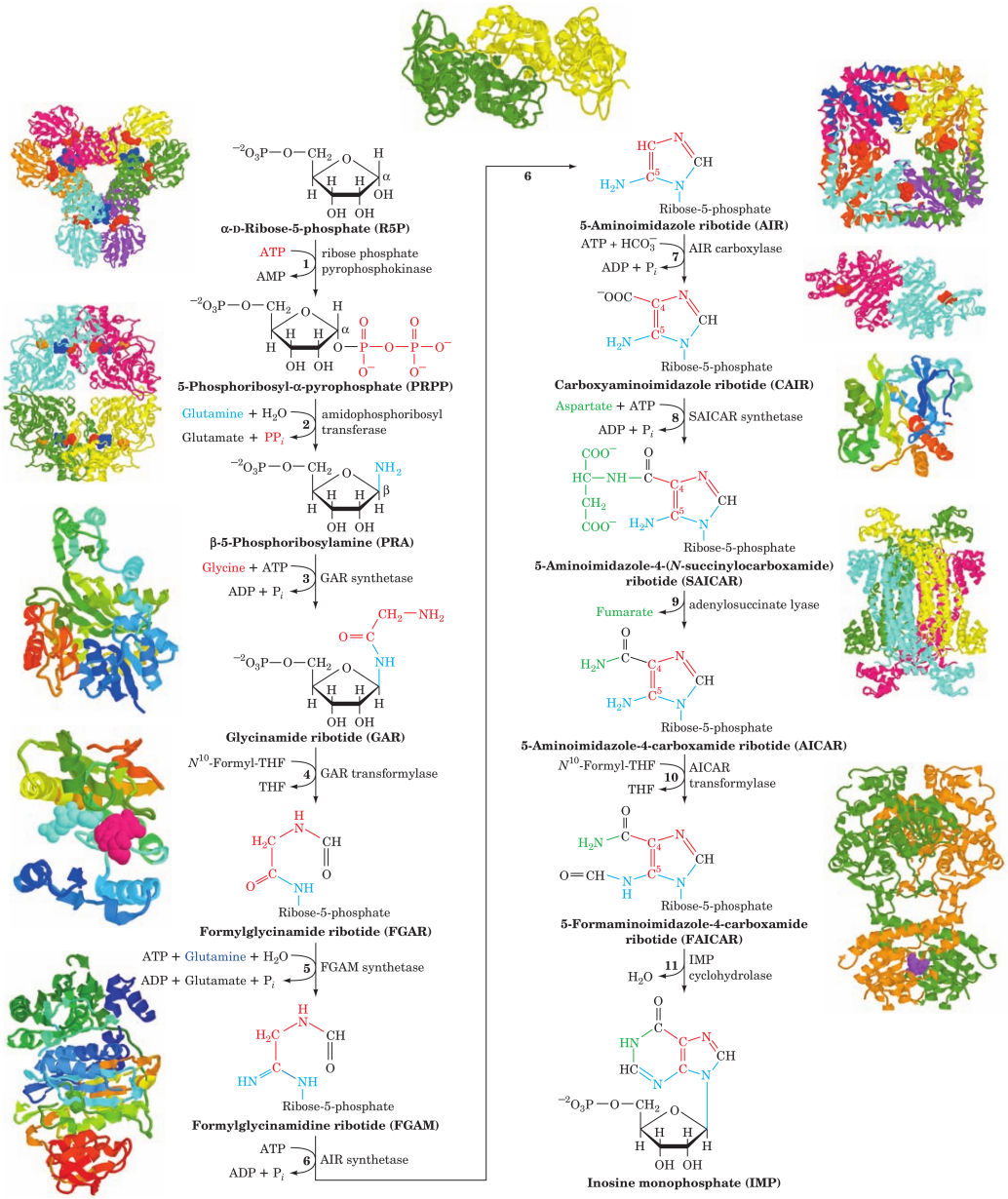
- phenformin



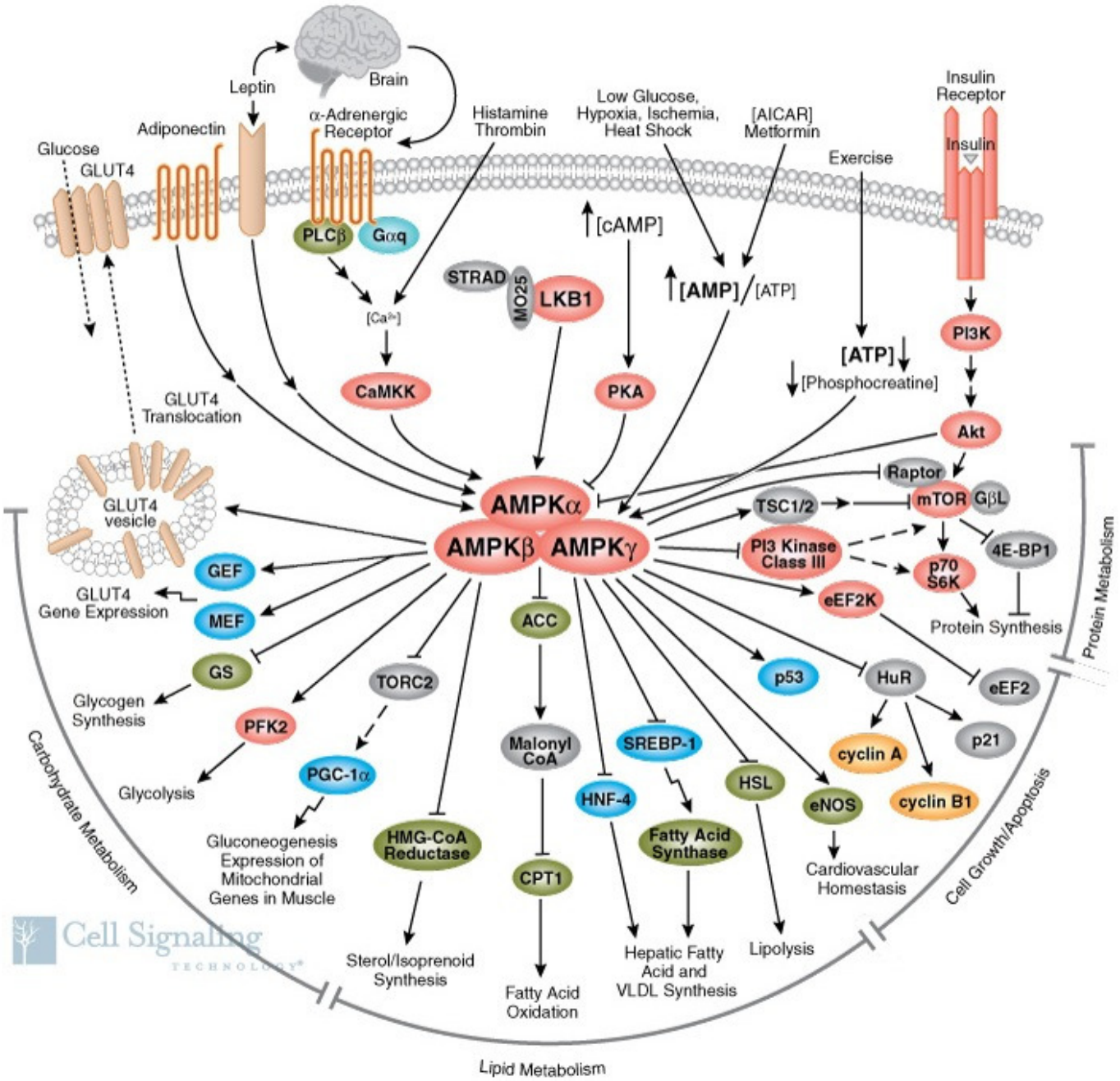
- thiazolidinedione



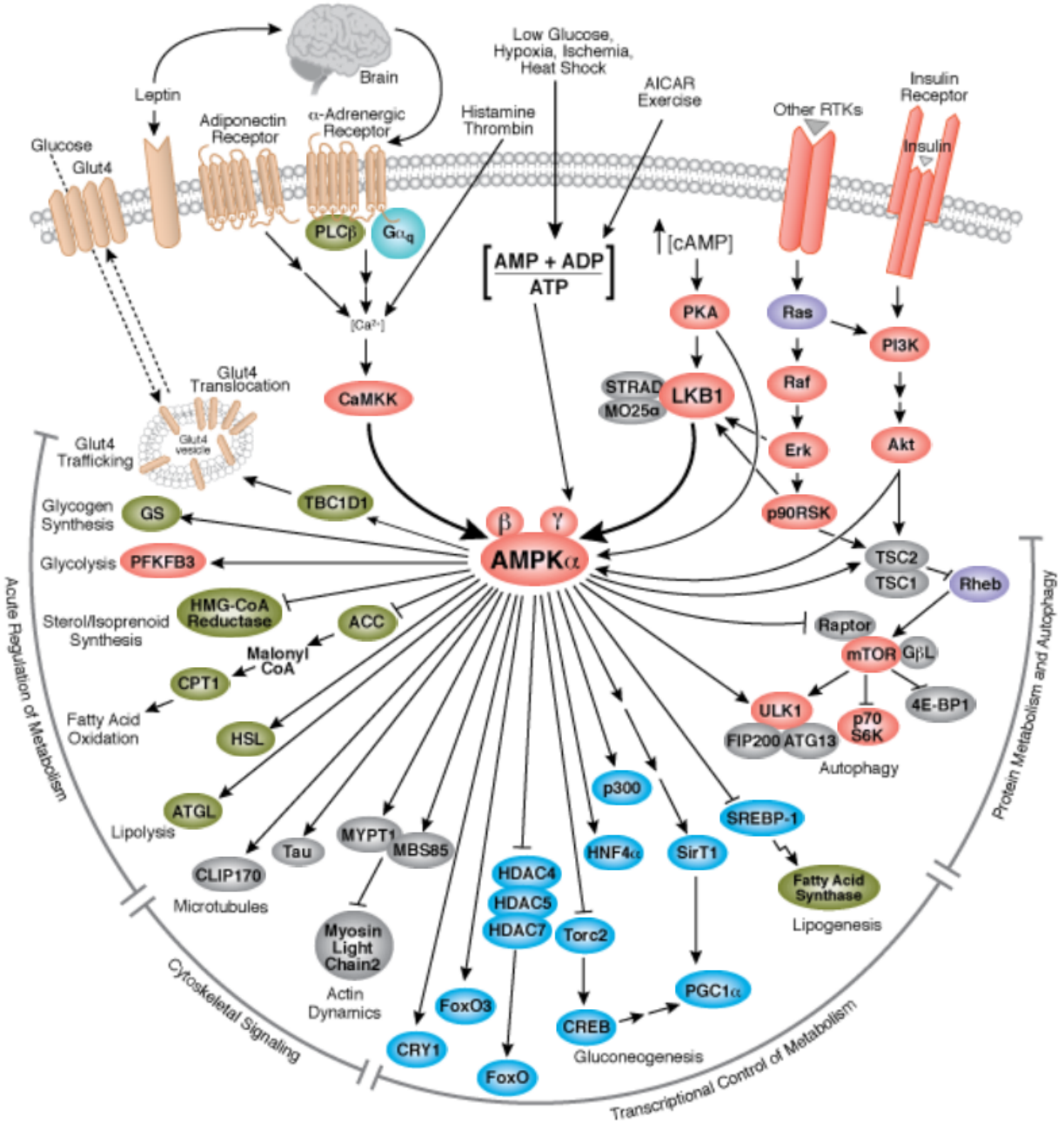
AICAR


α-D-Ribose-5-phosphate (R5P)
ATP
AMP
1
ribose phosphate pyrophosphokinase
5-Phosphoribosyl-α-pyrophosphate (PRPP)
Glutamine + H2O
Glutamate + PPi
2
amidophosphoribosyl transferase
β-5-Phosphoribosylamine (PRA)
Glycine + ATP
ADP + Pi
3
GAR synthetase
Glycinamide ribotide (GAR)
N10-Formyl-THF
THF
4
GAR transformylase
Ribose-5-phosphate
Formylglycinamide ribotide (FGAR)
ATP + Glutamine + H2O
ADP + Glutamate + Pi
5
FGAM synthetase
Ribose-5-phosphate
Formylglycinamidine ribotide (FGAM)
ATP
ADP + Pi
6
AIR synthetase
Ribose-5-phosphate
5-Aminoimidazole ribotide (AIR)
ATP + HCO3−
ADP + Pi
7
AIR carboxylase
Ribose-5-phosphate
Carboxyaminoimidazole ribotide (CAIR)
Aspartate + ATP
ADP + Pi
8
SAICAR synthetase
Ribose-5-phosphate
5-Aminoimidazole-4-(N-succinylocarboxamide) ribotide (SAICAR)
Fumarate
9
adenylosuccinate lyase
Ribose-5-phosphate
5-Aminoimidazole-4-carboxamide ribotide (AICAR)
N10-Formyl-THF
THF
10
AICAR transformylase
Ribose-5-phosphate
5-Formaminoimidazole-4-carboxamide ribotide (FAICAR)
H2O
11
IMP cyclohydrolase
Inosine monophosphate (IMP)

Summarizing scheme – by compound types



Summarizing scheme – signal mechanisms

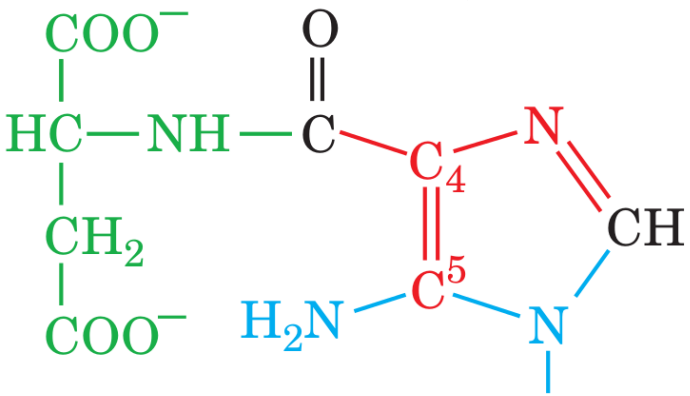


The End

KONEC – THE END – FIM – FIN – FINE – KONIEC

Thank you for your attention!

AICAR

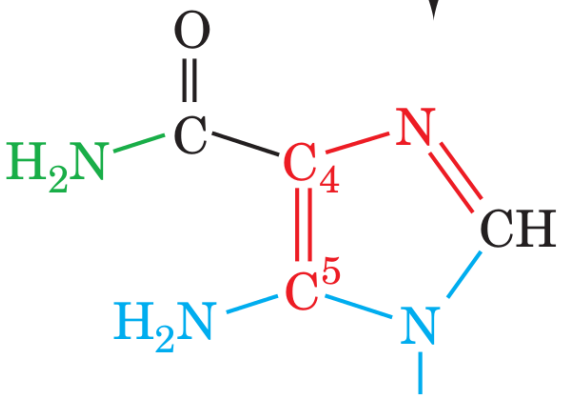


Ribose-5-phosphate

5-Aminoimidazole-4-(*N*-succinylocarboxamide) ribotide (SAICAR)

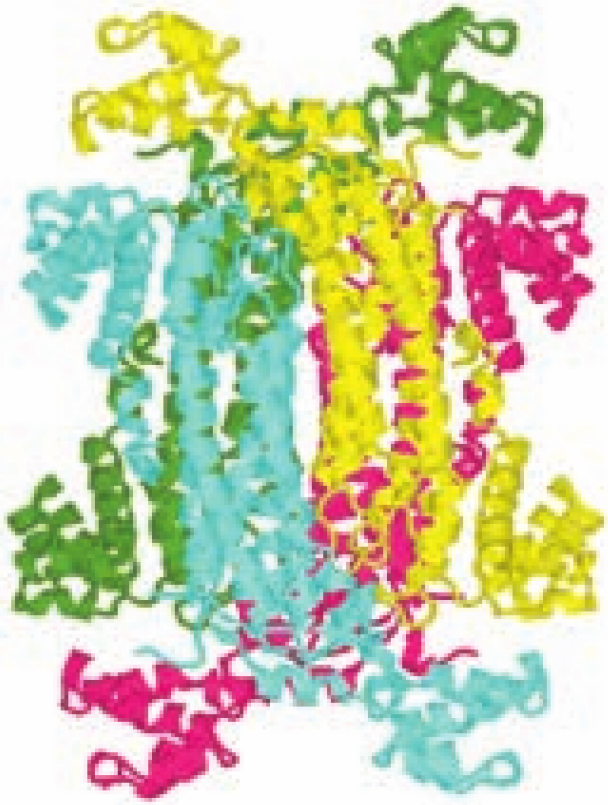
9 adenylosuccinate lyase

Fumarate



Ribose-5-phosphate

5-Aminoimidazole-4-carboxamide ribotide (AICAR)



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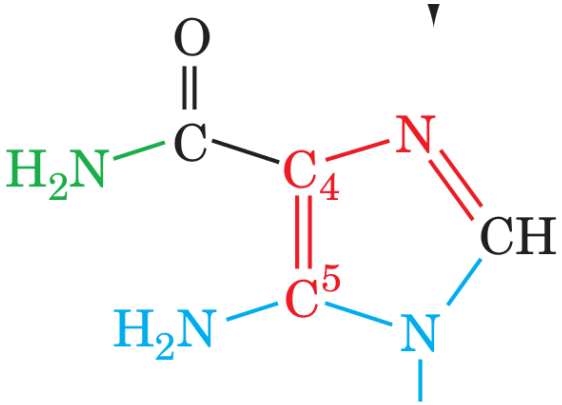
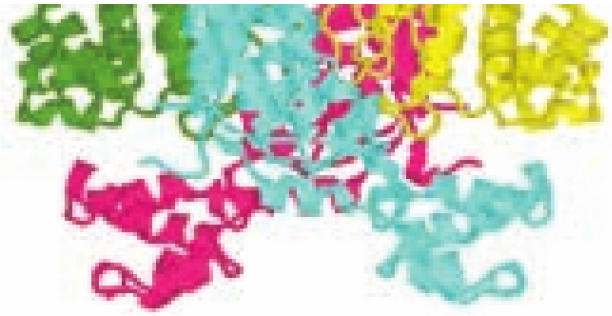
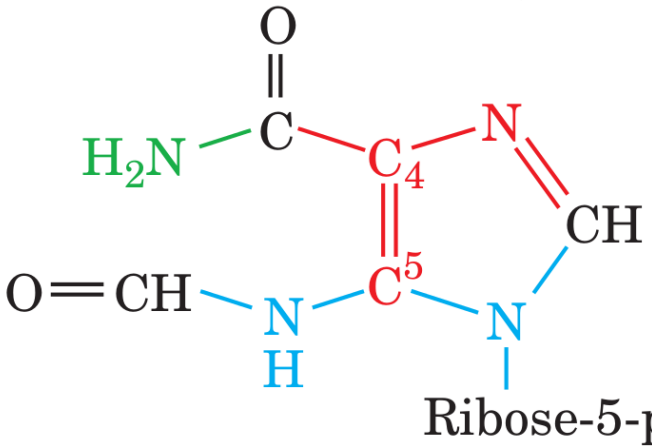




5-Aminoimidazole-4-carboxamide ribotide (AICAR)

N^{10}-Formyl-THF → THF (**10**) AICAR transformylase



5-Formaminoimidazole-4-carboxamide ribotide (FAICAR)