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Research Article

PREDICTING THE ACTIVITY OF ENZYMES UPON PHOSPHORYLATION/ DEPHOSPHORYLATION

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A B S T R A C T

A reversible covalent modification by Phosphorylation/Dephosphorylation of the key regulatory enzymes of various metabolic pathways is a well-established mechanism to regulate their activities soas to maintain body homeostasis. At the molecular level this reversible covalent modification is known to occur by a mechanism involving cAMP as a second messenger and cascade of enzymes. Some enzymes are known to become active while others inactive upon Phosphorylation or Dephosphorylation.The question that naturally arises is whether the selection of an enzyme to become either active or inactive upon hosphorylation or Dephosphorylation is a random phenomenon or is based upon some scientific evolutionary logic? A hypothesis has been proposed which based upon well established facts can help us to very easily predict which enzyme should become active or inactive upon Phosphorylation or Dephosphorylation.

INTRODUCTION

Key to the survival and maintenance of the homeostasis in the living systems lies in controlling various metabolic processes which in turn get regulated by controlling the efficiencies of the key regulatory enzymes. The efficiencies of the key regulatory enzymes can be controlled either by regulating their concentrations or their activities. The concentrations of the regulatory enzymes get controlled by regulating their rates of synthesis and or degradation; however, economically it is not a viable proposition (6).Activities of regulatory enzymes have been known to be regulated by allosteric effectors, binding with large molecular weight biomolecules and by covalent modifications which can either be reversible or irreversible. Over five hundred different types of covalent modifications have been found to take place in proteins. Most common modifying groups introduced are phosphoryl, acetyl, adenylyl, uridylyl, methyl amide, carboxyl, myristoyl, palmitoyl, prenyl, hydroxyl, sulfate and adenosine di phosphate ribosyl. Out of various ways of reversible covalent modifications, phosphorylation/ dephosphorylation is the most common mechanism adopted by living systems to regulate metabolic transformations and various other processes including gene expression and differentiation so that life can proceed with in well-defined limits (2-9,11).

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Southerland proposed that a cascade system of enzymes involving cAMP as a second messenger is required to cause reversible covalent modifications by phosphorylation/ dephosphorylation of key regulatory enzymes to produce a specific physiological response in response to internal or external stimuli. In his classical scheme, it was demonstrated that action of epinephrine in skeletal muscles and glucagon in liver/adipose tissue cause a net increase in blood glucose level as a result of phosphorylation/ dephosphorylation of key regulatory enzymes by a common cascade system (10). Review of literature (Journals and standard text Books) revealed that some enzymes are known to become active while others inactive upon Phosphorylation or Dephosphorylation, however, no explanation is available why an enzyme either should become active or inactive upon phosphorylation or dephosphorylation? A simple but logical hypothesis has been proposed to predict which enzyme should become active or inactive upon phosphorylatin or dephosphorylation.

DISCUSSION

Following are the well-established facts regarding regulating the activities of the key regulatory enzymes by reversible covalent modification with phosphorylation or dephosphorylation. "Action of epinephrine in skeletal muscles and glucagon in liver/Adipose tissue cause a net increase in blood glucose level as a result of phosphorylation of key regulatory enzymes using a common cascade system involving increase in cAMP."

Table Activities of key regulatory enzymes upon phosphorylation/ dephosphorylation

Serial No.	Major Metabolic Pathway	Key Regulatory enzymes	Upon phosphorylation Enzymes become Active	Inactive
1	Carbohydrate Catabolism			
	a) Glycolysis	i) Phosphofructokinase-1*		Yes
		ii) Pyruvate Kinase		Yes
	b) TCA Cycle	iii) Pyruvate dehydrogenase		Yes
	c) Pentose Phosphate Pathway**	-	-	-
	d) Glycogenolysis	iv) Phosphorylase	Yes	
		v) Phosphorylase kinase	Yes	
2	Carbohydrate Anabolism			
	a) Gluconeogenesis	vi) PEP Carboxy kinase	Yes	
		vii) Fructose16 Bisphosphatase	Yes	
	b) Glycogenesis	viii) Glycogen syntahase		Yes
3	Lipid Catabolism	ix) Hormonal sensitive lipase via Perilin	Yes	
4	Lipid Anabolism			
	a) Fatty acid biosynthesis	x) Acetyl CoA carboxylase		Yes
	b) Cholesterol biosynthesis	xi) HMG CoA-reductase		Yes
		xii) HMG CoA reductase kinase		
5	Amino Acid Catabolism			Yes
		xiii) Tyrosine 5 Monooxygenase	Yes	
6	Regulatory Enzymes/ Biomolecules			
		xiv) Phosphofructokinase-2		Yes
		xii) Phosphofructophosphatase-2	Yes	
		Inhibitor of phosphoprotein phosphatase	Yes	

Note:

i) * Indirectly controlled by Fructose-2,6 Bisphosphate (Allosteric activator).

ii) ** Activity of none of its regulatory enzymes is controlled by phosphorylation/dephosphorylation

iii) Upon dephosphorylation the activity pattern would be entirely opposite.

The Increase in blood glucose level would be a result of /lead to the following metabolic consequences

i. Decrease in oxidation/ utilization of glucose by glycolysis, TCA and Phosphopentose pathway.
ii. Decrease in glycogenesis
iii. Increase in glycogenolysis
iv. Increases in gluconeogenesis.
v. To meet obligatory energy requirements of the body,

Decrease in glucose oxidation would lead to the following

- Increase in lipolysis
- Decrease in lipogenesis
- Increase in protein and amino acids breakdown if the above situation gets prolonged.

Review of literature revealed that activities of the two enzymes or a tandem enzyme catalyzing opposite reactions get regulated by opposite mechanism e.g. If a specific Kinase gets activated by phosphorylation it's, corresponding phosphatase gets activated upon dephosphorylation (9).

The above facts prompted us to propose the following hypothesis: "Whether an enzyme should become active or inactive upon phosphorylation could easily be predicted keeping in view the fact that it must justify the resultant increase in blood glucose and its various resulting metabolic consequences".

In the following table, all the key regulatory enzymes of various metabolic pathways whose activities are known to be controlled by reversible covalent modification by phosphorylation/dephosphorylation are given. It is apparent from the following observations made from the table that the activities of the key regulatory enzymes upon phosphorylation/ dephosphorylation are in accordance with the proposed hypothesis.

1. Enzymes (i to v) involved in glucose utilization become inactive.
2. Enzymes involved in glucose formation (vi to viii) become active.
3. Enzymes involved in lipid breakdown (ix) become active.
4. Enzymes involved in lipid synthesis (X to xii) become inactive.
5. The activities of the regulatory enzymes (xiii to xv) are also in accordance with the predictions made based upon the proposed hypothesis.

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