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Pies and Fires Activate PAI-1 in Obesity and Diabetes Type 2

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Obesity is a global problem and is reaching pandemic proportion over the world. The supporting statistics are alarming and are indicating that the obesity and diseases associated with it will be one of the biggest public health challenges of the 21st century. This condition like many others is the result of interplay between genetic and environmental factors. Mutation in more than forty genes controls appetite and metabolism that predispose to obesity if sufficient food energy is delivered. In the last fifty years average per capita energy consumption rose from 2250 kcal to over 2750 kcal. This increase was partially due to reduction of hunger in many parts of the world but also substantially due to consumption of high energy food such as pies, fries and high sugar drinks.

Plasminogen Activator Inhibitor (PAI-1) is over expressed in obese people and in diabetes type 2. PAI-1 is a member of Plasminogen Activation System (PAS) that include: i) Plasminogen, a pro-enzyme activated by cleavage by urokinase (uPA) or tissue Plasminogen Activator (tPA), that in its active form is called plasmin. Plasmin digests variety of proteins of connective tissue and basement membranes and activates other latent proteolytic enzymes. ii) Activators - uPA and tPA. iii) Inhibitors of plasminogen activators. Four proteins have been identified as inhibitors of uPA or tPA, including PAI-1, PAI-2, PAI-3 and a protein nexin. Most relevant seems to be PAI-1, which exists in three different forms, the active, the non-active/latent and the cleaved form. PAI-1 is not a stable molecule and converts itself into the latent form (t½=1-2 h). During conversion the reactive loop (P10-P4') of PAI-1 is inserted into the central β-sheet of the protein molecule and the P1-P1' site is not accessible for reaction with tPA or uPA [6]. It has been found that visceral and subcutaneous adipose tissues express PAI-1 mRNA and expression is positively correlated with Body Mass Index (BMI). Also PAI-1 activity/antigen in plasma is positively and moderately associated with BMI. Moreover, PAI-1 over expression is reversible by weight reduction that substantially reduces plasma PAI-1 in obese people [2, 10]. Also, it was reported that the larger the fat cell size and the adipose tissue mass, the greater is the adipose production of PAI-1[10]. Furthermore, it has been found that PAI-1 expressed in different cell secreted by different human tissues exhibit heterogeneous glycosylation patterns. In lean individuals no glycans were detected on PAI-1 isolated from plasma, indicating that platelets synthesized this protein. But in obese people plasma PAI-1 had a glycan composition similar to that of adipose tissue indicating that it originated from the adipose cells [1]. It is very interesting that inhibitors of PAI-1 reduce dietary fat-induced obesity in animals. It was demonstrated in vivo that inhibition of PAI-1 in dose-dependent fashion reduces the body weight, adipocyte volume, and circulating active PAI-1 in plasma [2, 3]. In humans Loktionov et al. [7] found that tea significantly decreases PAI-1 activity. We have discovered that some theaflavins of black tea inhibit PAI-1 which may provide some explanation for the lower PAI-1 activity in tea lovers [5]. There is no clear explanation how

inhibition of PAI-1 can reduce body weight since PAI-1 regulates proteolysis. Nevertheless, Skurk et al. [10] have suggested following possibilities. PAI-1 may affect fat tissue growth by changing receptor-dependent transport of lipids into the lipocytes. Secondly, PAI-1 inhibition could inhibit angiogenesis that will reduce vascularization and consequently growth of the adipose tissue. Finally, inactivation of PAI-1 may stimulate migration of preadipocytes that would prevent their full differentiation into mature fat cells. Obesity is the major factor predisposing people to diabetes type two and PAI-1 is further over expressed in these patients. This elevation correlates with complications of diabetes. However, the link between insulin and the up-regulation of PAI-1 is unclear [4]. An elevated plasma level of PAI-1 mediates diabetic vascular complications and suggests diabetic nephropathy to be the major implication of PAI-1 high levels [8]. Nagi et al. provided the strongest evidence of contributory function of PAI-1 in diabetes complications. They found that Pima Indians with a very high rate of obesity and high rates of diabetes but surprisingly a low risk of ischemic heart disease and other diabetes complications. Interestingly in these ethnic groups PAI-1 activity is the same in non-diabetic and diabetic population [9]. It seems that increased circulating PAI-1 concentrations and activity are a hallmark of obesity and type 2 diabetes. Thus, PAI-1 deserves greater attention in assessment of prognosis and as a possible target to be eventually used in therapy.

Figure: 1

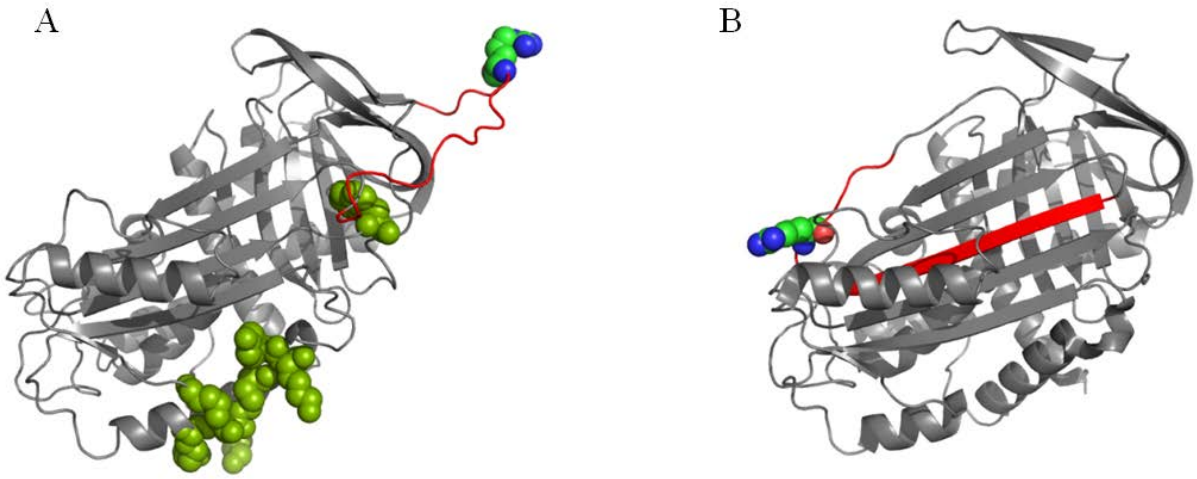

Figure 1: Ribbon model of active (A) and latent form of PAI-1. Glycans attached to active PAI-1 are shown in olive; arginine 369 of active site is shown as: green carbon, blue nitrogen, red oxygen. Tissue plasminogen activator and urokinase accept this amino acid into specificity pocket. In latent form Arg 369 is not accessible to uPA and tPA and activators cannot be inhibited. Active center loop is shown in red and this loop in latent form is inserted into the interior of molecule.

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