INSULIN-DEGRADING ENZYME AS A THERAPEUTIC TARGET FOR THE MANAGEMENT AND PREVENTION OF DIABETES

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Following its secretion from the pancreas, insulin levels are primarily determined by the rate of catabolism by proteolytic degradation and other processes. The principal protease responsible for the degradation and inactivation of insulin is insulin-degrading enzyme (IDE), an evolutionarily and structurally distinctive zinc-metalloprotease with many features that distinguish it from conventional zinc-metalloproteases. Following the discovery of IDE in 1949, there was considerable interest in the development of pharmacological inhibitors of IDE as anti-diabetic agents. Nevertheless, despite the great promise of this approach, and despite many attempts within both academia and private industry, inhibitors of IDE proved surprisingly elusive. Here we describe the development and characterization of the first small-molecule inhibitors of IDE. The unique properties of these compounds, including their ability to potentiate the action of insulin within cells, strongly suggest they will be valuable for the treatment and prevention of diabetes.