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Crystal Structure of Human Insulin-Regulated Aminopeptidase

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Dementia is the single greatest cause of disability in older Australians afflicting almost one in ten over the age of 65. In the absence of curative therapies, current treatments aimed at enhancing working memory target the cholinergic system and demonstrate limited efficacy, underpinning the need for a new class of cognitive enhancing drug. Insulin-regulated aminopeptidase (IRAP) is a membrane-bound zinc-metallopeptidase that cleaves neuroactive peptides in the brain and its inhibition gives rise to memory enhancing effects in both normal and memory-impaired rodents . Using a large scale insect cell expression system to produce milligram quantities of protein suitable for crystallography, and the Micro Crystallography Beamline at the Australian Synchrotron, we have determined the crystal structure of human IRAP to 2.96 Å. This structure revealed a semi-closed, four domain arrangement with a large, mostly buried cavity adjacent to the active site as well as a dimer interface located in the C-terminal domain. A comparison of the catalytic domain with related aminopeptidases revealed a strikingly different conformation of the GAMEN exopeptidase loop that explains IRAP's unique specificity for cyclic peptides such as oxytocin and vasopressin. This structure will be a powerful tool in the development of new classes of cognitive enhancers for treating memory disorders such as Alzheimer's dementia.

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Summary

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