S 17092: A Prolyl Endopeptidase Inhibitor as a Potential Therapeutic Drug for Memory Impairment. Preclinical and Clinical Studies

Philippe Morain, Pierre Lestage, Guillaume De Nanteuil, Roeline Jochemsen, Jean-Loïc Robin, David Guez, and Pierre-Alain Boyer

Institut de Recherches Internationales Servier, Courbevoie, France

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ABSTRACT

Any treatment that could positively modulate central neuropeptides levels would provide a promising therapeutic approach to the treatment of cognitive deficits associated with aging and/or neurodegenerative diseases. Therefore, based on the activity in rodents, S 17092 (2S,3aS,7aS)-1[[(R,R)-2-phenylcyclopropyl]carbonyl]-2-[(thiazolidin-3-yl)carbonyl]octahydro-1H-indole) has been selected as a potent inhibitor of cerebral prolyl-endopeptidase (PEP). By retarding the degradation of neuroactive peptides, S 17092 was successfully used in a variety of memory tasks. These tasks explored short-term, long-term, reference and working memory in aged mice, as well as in rodents and monkeys with chemically induced amnesia or spontaneous memory deficits. S 17092 has also been safely administered to humans, and showed a clear peripheral expression of its mechanism of action through its inhibitory effect upon PEP activity in plasma. S 17092 exhibited central effects, as evidenced by EEG recording in healthy volunteers, and could improve a delayed verbal memory task. Collectively, the preclinical and clinical effects of S 17092 have suggested a promising role for this compound as an agent for the treatment of cognitive disorders associated with cerebral aging.