[PA1-13] [04/20/2001 (Fri) 10:30 - 11:30 / Hall 4]

A New Class of Potent Cathepsin K Inhibitors; OST-1857 Derivatives

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Cathepsin K(CK) is highly and selectively expressed within osteoclasts and has been proposed to play an important role in bone resorption. CK has emerged as a potential target for the treatment of osteoporosis. In order to discover potent and selective cathepsin K inhibitors, OST-1857 was identified as a potent and reversible inhibitor of cathepsin K with a Ki value of 24 nM. In bone resorption assay system, OST-1857 suppressed the resorption pit formation and the release of CTx from ivory slices in the dose dependent manner. Oral or intravenously administered OST-1857 also inhibited PTH-dependent increase of blood calcium level in thyroparathyroidectomized (TPTX) rats with ED50 values of 3.6 mg/kg (iv) and 77.4 mg/kg (po).
Modification of this lead compound by replacement of substituents increased the potency of the inhibitor by 100-fold and the selectivity against other cathepsin subtypes such as Cathepsin B, C, D, H, L, G, and S.
In this presentation, it will be introduced a new class of cathepsin K inhibitors, OST-1857 derivatives, efficiently suppress the bone resorption in vitro and in vivo. It could be a promising therapeutic agent for the treatment of diseases of excessive bone loss such as osteoporosis.
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[PA1-14] [04/20/2001 (Fri) 10:30 - 11:30 / Hall 4]

Cocaine Administered into the mPFC Reinstates Cocaine-Seeking Behavior by Increasing Glutamate and Dopamine Transmission in the Nucleus Accumbens in Rats

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One of the major determinants of reinstatement of cocaine use among human addicts is acute re-exposure to the drug, which often precipitates cocaine craving and relapse. We used an animal model of cocaine relapse in order to determine the anatomical and pharmacological determinants of reinstatement of cocaine-seeking behavior following a cocaine priming injection. Systemic injection of cocaine as well as microinjections of this drug into either the nucleus accumbens or medial prefrontal cortex (mPFC) reinstated previously extinguished drug-seeking behavior. In addition, administration of an AMPA, D1-like or D2-like antagonist into the nucleus accumbens blocked intra-mPFC-induced reinstatement of
cocaine seeking; intra-accumbal administration of an NMDA antagonist failed to influence reinstatement to a cocaine priming injection in the mPFC. These data indicate that the nucleus accumbens and mPFC play important roles in cocaine priming-induced reinstatement. Moreover, intra-mPFC cocaine promotes reinstatement of cocaine seeking by increasing glutamate and dopamine transmission in the nucleus accumbens.