In vivo evaluation of effects of various histamine H_3 receptor inverse agonists on methamphetamine-induced hyperlocomotion and stereotyped behavior in mice

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Pretreatment of mice with pitolisant, a histamine H_3 receptor antagonist, showed a significant reduction of the hyperlocomotion induced by METH, as compared with vehicle (saline)-pretreated subjects. The pitolisant action on METH-induced hyperlocomotion was completely abolished by a histamine H_1 receptor antagonist pyrilamine resulting in hyperlocomotion, but not by a peripherally acting histamine H_1 receptor antagonist fexofenadine, a brain-penetrating histamine H_2 receptor antagonist zolantidine, or a brain-penetrating histamine H_4 receptor antagonist JNJ -7777120. Pretreatment with a histamine H_3 receptor agonist immepip rather augmented METH (3 mg/kg)-induced behavioral abnormalities from hyperlocomotion to stereotyped biting, and, combined pretreatment of pitolisant with immepip significantly attenuated the stereotyped behaviors. Pretreatment with JNJ-10181457 or conessine, other histamine H_3 receptor antagonists, showed inhibitory effects on METH-induced hyperlocomotion similar to that of pitolisant. No significant change in locomotion was observed in mice pretreated with pitolisant, JNJ-10181457, or conessine alone. Pretreatment with pitolisant prior to a high-dose METH (10 mg/kg) significantly decreased the intensity of stereotyped behaviors and increased its latency to onset in a dose-dependent manner. JNJ-1018145, but not conessine, mimicked the inhibitory action on METH-induced stereotyped behavior.