Histamine H₃ receptor inverse agonists alleviate methamphetamine-induced behavioral abnormalities in mice via histamine H₁ receptors

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Background: Due to its highly addictive properties, and the adverse consequences associated with acute and chronic use of methamphetamine (METH), effective treatments for METH dependence are needed. Unfortunately, various attempts at pharmacotherapy trials have yielded unpromising and inconsistent results using medications developed to date. Several novel alternative approaches have been a matter of intense investigation more recently, including dopamine D₃ receptor antagonists and partial agonists, and manipulations of brain histamine systems. The later possibility is addressed in this presentation.

Methods: We investigated whether pretreatment with histamine H₃ receptor inverse agonists such as pitolisant and JNJ-10181457 affected METH-induced hyperlocomotion and stereotypy in male ICR mice. Locomotor activity was measured by Animex Auto. Quantification of the incidence of stereotyped behavior was made by trained observers blinded to the experimental conditions.

Results: A single administration with METH (3 mg/kg, i.p.) induced hyperlocomotion in mice. Pretreatment of mice with pitolisant or JNJ-10181457 showed a significant reduction of the hyperlocomotion induced by METH, as compared with vehicle- (saline) pretreated subjects. No significant change in locomotion was observed in mice pretreated with H₃ receptor inverse agonists alone. Pretreatment with pitolisant or JNJ-10181457 prior to a high-dose METH (10 mg/kg, i.p.) significantly decreased the intensity of stereotyped behaviors and increased its latency of onset in a dose-dependent manner. The pitolisant action on METH-induced hyperlocomotion was completely abolished by a histamine H₁ receptor antagonist pyrilamine, but not by a brain-penetrating histamine H₂ receptor antagonist zolantidine.

Conclusions: These observations suggest that pretreatment with H₃ receptor inverse agonists attenuate METH-induced behavioral abnormalities via the histamine receptor subtype H₁, but not H₂, and support the idea that activation of brain histamine systems may be a good strategy for the development of agents which treat METH abuse and dependence.