Modulatory function of the H_3 histaminergic receptor system in addiction: an example with cocaine and ethanol

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The histaminergic neurotransmission is involved in many biological functions, including the modulation of arousal, fluid balance, food intake, reinforcement and learning. Recently, the results of several studies have also suggested that the central histaminergic system, and particularly the H_3 receptors, plays a role in drug addiction. For example, in animal experiments, the administration of H_3 agonists and antagonists modulate the self-administration of various drugs including cocaine, amphetamine and alcohol. In the present studies, we used the locomotor stimulant effects of drugs as an index of their abuse potential (most of addictive drugs stimulate locomotor activity, at least at some doses, and this effect is often considered as an intrinsic feature of drug addiction). In two independent experiments, we tested the effects of thioperamide, a histamine H_3 antagonist/inverse agonist, on the locomotor stimulant effects of cocaine and ethanol. Our results show that thioperamide modulates the locomotor stimulant effects of both cocaine and ethanol. However, this modulatory effect was surprisingly opposite in direction depending upon the tested drug. Whereas thioperamide potentiated the locomotor stimulant effect of cocaine, it prevented the hyperactivity induced by 2 g/kg ethanol in mice. In the brain, H_3 receptors is both a histamine autoreceptor modulating the synaptic release of histamine and a heteroreceptor that modulates the release of other neurotransmitters such as dopamine, acetylcholine and GABA. It is therefore likely that the modulatory action of thioperamide on cocaine and ethanol stimulant effects involves different neurotransmitter system. This conclusion is supported by our preliminary results on knock-out mice genetically devoid of histamine. In such knock-out mice, ethanol retains its stimulant properties, suggesting that histamine release is not involved in this effect. In contrast, these knock-out mice showed a reduced cocaine-induced hyperactivity, indicating that histamine release play a significant role in the stimulant effect of cocaine.