Modulatory function of the H₃ 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 H₃ receptors, plays a role in drug addiction. For example, in animal
experiments, the administration of H₃ 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 H₃ 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, H₃ 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.