Titre:

Simultaneous blockade of α1b-adrenergic and 5HT2A-serotonergic receptors for the treatment of AUD. Cocktail: Pharmacological rationale.

Co-auteurs:

J.P. Tassin, Inserm, Sorbonne Université, Kinnov Therapeutics, Paris, France

F. Trovero, Kinnov-Therapeutics, Orléans, France

P. Bernard, Kinnov-Therapeutics, Orléans, France

Cocktail group, Kinnov-Therapeutics, Orléans, France.

Auteur principal:

Jean-Pol Tassin, Inserm, Sorbonne Université, Kinnov-Therapeutics, Paris, France.

Mobile : 0670747783 e-mail : jean-pol.tassin@upmc.fr

Description des résultats:

Alcohol-dependence is a chronic disease with a dramatic and expensive social impact. A challenge in drug dependence is to delineate long-term behavioural and neurochemical modifications induced by drugs of abuse. In rodents, drugs of abuse induce locomotor hyperactivity, and repeating injections enhance this response. This effect, called behavioural sensitization, persists many months after the last administration, thus mimicking long-term sensitivity to drugs observed in human addicts. Although addictive properties of drugs of abuse are generally considered to be mediated by an increased release of dopamine in the ventral striatum, we have shown that the development and the expression of behavioural sensitization to most drugs of abuse were under the control of two monoaminergic receptors, the α1b-adrenergic and 5-HT2A receptors. This led us to propose that the repeated consumption of drugs of abuse could, through repeated activations of noradrenergic and/or serotonergic neurons, uncouple a mutual control between the two systems, over-activation of noradrenergic systems being implicated in craving whereas serotonergic ones would control impulsivity. In line with this concept, we made the hypothesis that repeated treatments with specific antagonists of both noradrenergic and serotonergic receptors may facilitate a re-coupling of these systems and, thus, possibly intervene on withdrawal and relapse. This hypothesis was tested in mice rendered dependent to alcohol following 10 days of forced alcoholic (10 %) consumption. We found that a combination of prazosin (0.5 mg/kg, an α1b-adrenergic antagonist) and cyproheptadine (1 mg/kg, a 5-HT2A antagonist) could

reverse alcohol preference in these mice. Interestingly, each component alone did not exhibit any significant effect. Altogether these findings strongly suggest that combined prazosin and cyproheptadine could be efficient as a therapy to treat alcoholism in humans.

Pas de conflit d'intérêt autre que Kinnov-Therapeutics.