

Trace amine-associated receptor 1 activation reduces alcohol drinking and normalizes dopamine signaling under glutamatergic dysregulation and adolescent alcohol exposure

Co-authors' contact details

C. Rouanet, Groupe de Recherche sur l'Alcool et les Pharmacodépendances, Université de Picardie Jules Verne, Amiens, France

M. Lamarche, Groupe de Recherche sur l'Alcool et les Pharmacodépendances, Université de Picardie Jules Verne, Amiens, France

V. Debuyscher, Groupe de Recherche sur l'Alcool et les Pharmacodépendances, Université de Picardie Jules Verne, Amiens, France

G. Fouquet, Groupe de Recherche sur l'Alcool et les Pharmacodépendances, Université de Picardie Jules Verne, Amiens, France

J. Orzelska-Górka, Department of Pharmacology and Pharmacodynamics, Medical University of Lublin, Lublin, Pologne

M. Kruk-Slomka, Department of Pharmacology and Pharmacodynamics, Medical University of Lublin, Lublin, Pologne

G. Biała, Department of Pharmacology and Pharmacodynamics, Medical University of Lublin, Lublin, Pologne

V. Bouet, COMETE, Université de Caen Normandie, Caen, France

T. Freret, COMETE, Université de Caen Normandie, Caen, France

M. Boulouard, COMETE, Université de Caen Normandie, Caen, France

D. Leo, Groupe de Recherche sur l'Alcool et les Pharmacodépendances, Université de Picardie Jules Verne, Amiens, France

J. Jeanblanc, Groupe de Recherche sur l'Alcool et les Pharmacodépendances, Université de Picardie Jules Verne, Amiens, France

M. Naassila, Groupe de Recherche sur l'Alcool et les Pharmacodépendances, Université de Picardie Jules Verne, Amiens, France

Contact details of the corresponding author for the Congrès de l'ALBATROS

Charles Houdant, Groupe de Recherche sur l'Alcool et les Pharmacodépendances, Université de Picardie Jules Verne, Amiens, France, charles.houdant@u-picardie.fr

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Objectives

Glutamatergic and dopaminergic dysregulations are core features of alcohol use disorder (AUD) and schizophrenia, yet no treatment is currently effective for their comorbidity. Trace amine-associated receptor 1 (TAAR1), which modulates both systems, has emerged as a promising therapeutic target with preclinical efficacy in schizophrenia, but its relevance for AUD remains insufficiently characterized. We therefore investigated whether TAAR1 activation reduces alcohol drinking and prevents ethanol-induced dopaminergic alterations under both healthy (normal) conditions and in a genetic model of glutamatergic dysregulation.

Materials and methods

Alcohol intake was assessed in two complementary mouse models: adult male C57BL/6JRj mice under physiological conditions, and adult male serine racemase knock-out (SRKO) mice previously exposed to alcohol during adolescence, a genetic model of chronic NMDA receptor hypofunction. *Ex vivo* fast-scan cyclic voltammetry was used to measure dopamine release in the nucleus accumbens (NAc) core. The effects of the full TAAR1 agonist RO5166017 on alcohol consumption and dopamine release were then evaluated in both models.

Results and conclusion

In C57BL/6JRj mice, RO5166017 reduced alcohol intake, while exerting opposite effects on dopamine release depending on prior alcohol exposure: it decreased dopamine release in control animals but increased it in alcohol-exposed mice. SRKO mice exposed to alcohol during adolescence consumed less alcohol in adulthood, a phenotype associated with a blunted dopaminergic response to acute ethanol and enhanced sensitivity to the TAAR1 full agonist RO5166017, which robustly reduced alcohol consumption and normalized dopamine signaling. Together, these findings support a coherent behavioral-neurochemical framework in which TAAR1 activation reduces alcohol drinking and normalizes dysregulated dopaminergic transmission, particularly under conditions of glutamatergic alteration and adolescent alcohol exposure. By restoring dopaminergic and glutamatergic communication, TAAR1 activation could offer a new therapeutic avenue for schizophrenia–AUD comorbidity. These findings therefore provide a solid foundation for our ongoing work investigating whether TAAR1 activation can counteract functional connectivity deficits in schizophrenia–AUD comorbidity.