

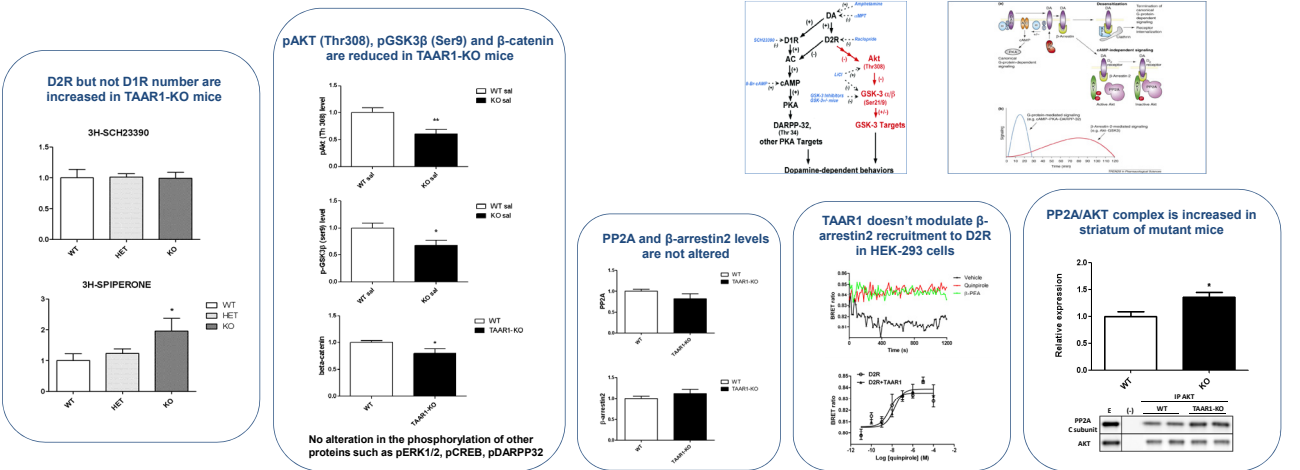
Role of Trace amine-associated receptor 1 (TAAR1) in the modulation of dopaminergic system and cortico-striatal signaling

S. Espinoza¹, I. Sukhanov¹, G. Lignani¹, L. Medrihan¹, S. Maggi¹, G. Giannotti², F. Fumagalli², F. Benfenati¹, V. Tucci¹, R. Gainetdinov¹
¹Italian Institute of Technology, NBT, Genova, Italy ²University of Milan, Pharmacology, Milan, Italy

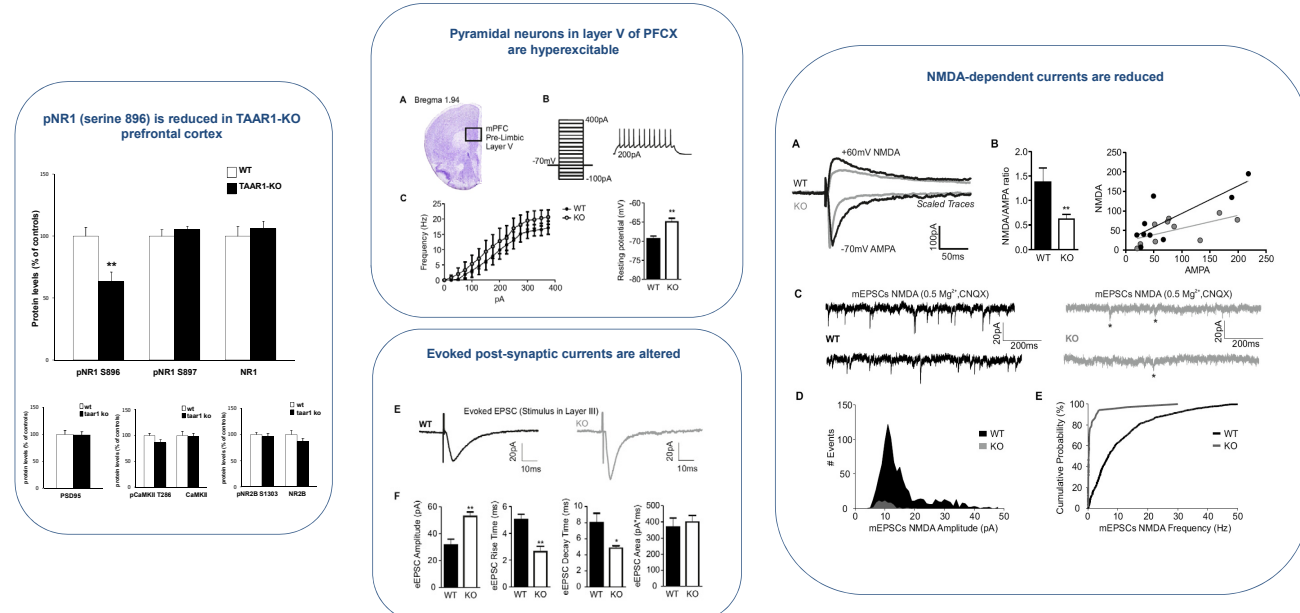
Introduction

Mammalian Trace Amine Associated Receptor 1 (TAAR1) is a G protein-coupled receptor (GPCR) that is mainly expressed in limbic regions and monoaminergic nuclei, such as ventral tegmental area, dorsal raphe and nucleus coeruleus (Borowsky et al., 2001; Bunzow et al., 2001). TAAR1 can be activated by several members of a class of endogenous biogenic amines called "trace amines" (TAs) that includes β-phenylethylamine (β-PEA), p-tyramine, octopamine, tryptamine as well as by several compounds known to target monoaminergic transmission such as amphetamine and some of its derivatives (Grandy, 2007). There is evidence indicating that TAAR1 could be involved in modulation of dopaminergic function (Sotnikova et al., 2009). In mice lacking TAAR1 (TAAR1-KO mice), amphetamine induces more pronounced locomotor stimulation and dopamine release (Volinska et al., 2007). Moreover, it has been reported that D2 receptor function is altered in TAAR1-KO mice (Espinoza et al., 2011). Dopamine system is involved in many physiological functions and has been implicated in various pathological states such as schizophrenia and Parkinson's disease. Therefore, understand the TAAR1 role in the modulation of dopamine system could help to better comprehend of the etiology of these diseases and maybe to discover new pharmacological approaches to cure them.

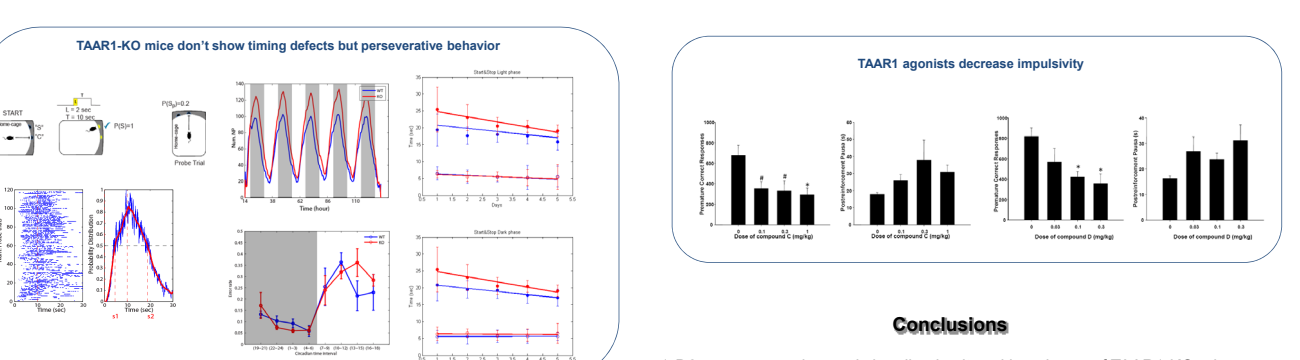
STRIATUM



PF CX



Behavior



Conclusions

1. D2 receptor number and signaling is altered in striatum of TAAR1-KO mice
2. NMDA functions are reduced in prefrontal cortex
3. TAAR1 correct function seems important for fronto-striatal related behavior

References

Borowsky B, Adham N, Jones KA, Raddear T, Arimura H, Ogozalek KL, Durkin MM, Lachyri PP, Bovee S, Boyle N, Xu X, Kouranova E, Lichtow H, Ochoa FV, Blanchet TA and Gerad C (2001) Trace amine identification of a family of mammalian G-protein-coupled receptors. *Proc Natl Acad Sci U S A* 98(11):6968-6972.

Erkula A, Tuohi O, Sillanpaa M, Nopola-Hemmi H, Oksanen J, Vartiainen J, Pirttila J, Burch D, Casanovi M, Hoener MC and Beller B (2009) The selective antagonist EPPTB reveals TAAR1-mediated regulatory mechanisms in dopaminergic neurons of the mammalian system. *Proc Natl Acad Sci U S A* 106(12):5000-5005.

Erkula A, Sillanpaa M, Aramianpour S, Hanson LM, Zhang Q, Doherty D, Daniel T, Sotnikova K, Puumala M, Kennedy J, Olson SB, Magens RE, Amara SG and Grandy DK (2001) Amphetamine, S-1-methylphenethylamine, amphetamine, and metabolites of the catecholamine neurotransmitters are agonists of a rat trace amine receptor. *Mol Pharmacol* 60(6):1181-1188.

Grandy DK (2007) Trace amine-associated receptor 1: Family archetype or iconoclast? *Pharmacol Ther* 114(2):355-360.

Volinska TD, Caron MG and Gainetdinov RR (2005) Trace amine-associated receptors as emerging therapeutic targets. *Adv Pharmacol* 62(2):229-256.

Volinska TD, Swanson CJ, Smith KE, Zhang H, Borowsky B, Seaman P, Blanchet T and Gerad CP (2007) The Trace Amine 1 receptor knockout mouse: an animal model for relevance to schizophrenia. *Genes Brain Behav* 6(1):62-69.

Espinoza S, Sukhanov I, Medrihan L, Maggi S, Giannotti G, Fumagalli F, Benfenati F, Tucci V, Gainetdinov R (2011) Functional interaction between Trace Amine Associated Receptor 1 (TAAR1) and dopamine D2 receptor. *Mol Pharmacol* 2011 Jan 15