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EXCITING TOPICS INCLUDE

- Trace Amine-Associated Receptor 1 (TAAR1): from cell to clinic
- Adult neurogenesis in anxiety and mood disorders
- Personalised treatment of major depression
- New European pharma research initiatives
- Neuropeptides, obesity and addiction
- Neurobiology of ADHD across the lifespan

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S.03.04 FGFR1–5-HT$_{1A}$ receptor heterocomplexes: relevance for neuroplasticity and depression

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The hippocampal atrophy consistently found in major depression may be involved in the pathophysiology of this disease in view of its critical role in the emotional networks. Evidence is given for the existence of FGFR1–5-HT$_{1A}$ heteroreceptor complexes which are involved in neuroplasticity in the hippocampus using the proximity ligation assay with a partial interface characterization [1]. The participation of 5-HT$_{1A}$ and FGFR1 homodimers and recruitment of β-arrestin2 was demonstrated in the FGFR1–5-HT$_{1A}$ heteroreceptor complexes upon agonist treatments [2]. Co-activation of the two protomers also resulted in synergistic increases in extensions of PC12 cells and neurite densities and protrusions in primary hippocampal cultures dependent on the receptor interface. We have also found that acute and a 10 day i.c.v. treatment with FGF-2 and the 5-HT$_{1A}$ agonist 8-OHDPAT in the Sprague-Dawley rat can produce synergistic antidepressant effects in the forced swim test. Thus, this cotreatment may result in more rapid and stronger antidepressant-like actions than found with SSRIs. Evidence is also presented for the existence of FGFR1–5-HT$_{1A}$ heteroreceptor complexes in the mesencephalic raphe 5-HT nerve cells [3]. The raphe 5-HT$_{1A}$ autoreceptor when being part of the FGFR1–5-HT$_{1A}$ heteroreceptor complex may therefore have a beneficial role in depression by assisting in the recovery of 5-HT nerve cell trophism from a state of atrophy including increased 5-HT synthesis and storage. The findings indicate that neurotrophic and antidepressant effects of 5-HT may, in part, be mediated by activation of the 5-HT$_{1A}$ receptor protomer in the hippocampal FGFR1–5-HT$_{1A}$ receptor complex enhancing the FGFR1 signaling.

References

[1] Borroto-Escuela DO, Romero-Fernandez W, Mudo G et al., 2012 Fibroblast growth factor receptor 1 – 5-hydroxytryptamine 1A heteroreceptor complexes and their enhancement of hippocampal plasticity. Biological psychiatry 71, 84–91.
[2] Borroto-Escuela DO, Corrales F, Narvaez M et al., 2013 Dynamic modulation of FGFR1–5-HT$_{1A}$ heteroreceptor complexes. Agonist treatment enhances participation of FGFR1 and 5-HT$_{1A}$ homodimers and recruitment of beta-arrestin2. Biochemical and biophysical research communications 441, 387–392.
[3] Borroto-Escuela DO, Romero-Fernandez W, Perez-Alea M et al., 20124 The existence of FGFR1–5-HT$_{1A}$ receptor heterocomplexes in midbrain 5-HT neurons of the rat: relevance for neuroplasticity. Current Protein & Petides Science In Press.

S.04. Trace Amine-Associated Receptor 1 (TAAR1): from cell to clinic

S.04.01 Discovery of the trace amine-associated receptor (TAAR)

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In 1909 the noncatecholic biogenic amines phenylethylamine and tyramine were shown to produce robust cardiovascular effects in mammals. With the discovery of synephrine, octopamine and tryptamine throughout the animal kingdom the trace amines as they came to be known enjoyed widespread attention from physiologists and neuroscientists for more than 50 years until receptors for their relatives dopamine, norepinephrine and serotonin were cloned in the mid-1980s. During the 15 years that followed no trace amine receptor was discovered and the field slid into relative obscurity. Then, in 2001 two groups using related but different methodological approaches reported discovery of an orphan $G_{alpha}s$ protein-coupled receptor [1] that is activated by trace amines and is now referred to as trace amine-associated receptor 1 (TAAR1) [2]. Progress toward understanding the biology of TAAR1 in health and disease was initially slow due to a complete lack of animal models, antibodies and selective pharmacologic tools. However, with the recent availability of mouse lines lacking *taar1*$^{-/-}$ as well as the TAAR1-selective antagonist EPPTB [3] it has become possible to explore the role(s) of TAAR1 *in vivo*. Using a line of TAAR1-deficient mice generated at UC Davis and EPPTB made in-house we have taken a translational approach to exploring the contribution of TAAR1-mediated signaling to the physiological and behavioral effects of cocaine, methamphetamine and bupropion. Based on our results we conclude methamphetamine-activated TAAR1-mediated signaling accounts for ~70% of the drug's stimulatory effect on locomotion in mice with the remaining 30% due to its interference with dopamine transport.

References

[1] Grandy, D.K. 2007 Trace amine-associated receptor 1-Family archetype or iconoclast? Pharmacology and Therapeutics 116, 355–390.
[2] Lindemann, L., Ebeling, M., Kratochwil, N.A., Bunzow, J.R., Grandy, D.K., Hoener, M.C. 2005 Trace amine associated receptors form structurally and functionally distinct subfamilies of novel G protein-coupled receptors. Genomics 85, 372–385.
[3] Bradaia, A., Trube, G., Stalder, H., Norcross, R.D., Ozmen, L., Wettstein, J.G., Pinard, A., Buchy, D., Gassmann, M., Hoener, M.C., Bettler, B. 2009 The selective antagonist EPPTB reveals TAAR1-mediated regulatory mechanisms in dopaminergic neurons of the mesolimbic system. Proceedings of the National Academy of Science, USA 106, 20081–20086.

S.04.02 Molecular modulation of dopamine transmission by TAAR1

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G protein-coupled Trace Amine-Associated Receptor 1 (TAAR1) is emerging as a promising new drug target for psychiatric disorders. Recent progress in identifying selective ligands for TAAR1 led to the possibility of evaluation of the functional consequences