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In Vivo Significance of In Vitro Studies on G-Protein-Coupled Receptor Heteromers

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Interactions between distinct receptor proteins have been assessed *in vitro* and *in vivo*. Among these studies are G-Protein-Coupled Receptor (GPCR) heteromers. GPCR heteromers form a popular area for study in molecular pharmacology and are expected to contribute valuable information to clinical needs for development of medications discovery in various neuropsychiatric diseases and symptoms. For example, physical formation of GPCR heteromers could result in a novel signaling mechanism that is distinct from those of individual GPCR monomers or their homomer. However, significance of various studies on dopamine (DA) D_1/D_2 receptor heteromers was challenged by a recent report [1]. Javitch et al. [1] provided compelling evidence against D_1/D_2 heteromers, one of the most prominent subjects of interest in neuropsychiatry field.

In the study Javitch et al. performed an "*in vivo*" assessment of the first demonstration for the presence of DA D_1/D_2 receptor heteromers in animal tissues [1]. Surprisingly, despite the successful creation of DA D_1/D_2 receptor heteromers "*in vitro*", their immunohistochemical studies discovered the virtual absence of physical DA D_1/D_2 receptor heteromers in the shell region of the nucleus accumbens (NAS) from C57Bl/6J mouse brain [1]. In the NAS, DA D_1 and D_2 receptors seem to co-express in the same neuron for some neurons but did not localize [1]. The virtual absence of physical DA D_1/D_2 receptor heteromers "*in vivo*" was further substantiated by the discovery of lack of localization across species. For example, there was little if any signal indicative of the presence of DA D_1/D_2 receptor heteromers in the NAS from a rat and the ventral striatum from rhesus monkey. Since various drugs abused by humans are known to increase extracelluar DA levels in the NAS, the "*in vivo*" negative results against the presence of DA D_1/D_2 receptor heteromers in the NAS could have a substantial impact at least on research for drug abuse.

In sumary, the failure to demonstrate *in vivo* the presence of DA D_1/D_2 receptor heteromers [1] undoubtly suggests reconsideration of the use of the "*in vitro* preclinical" models using receptor couplings. There is a clear need to reassess the validity of this approach for the development of medications discovery regarding various neuropsychiatric diseases and symptoms.

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