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MEETING ABSTRACT

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On the existence of multiple A2A, D2 and sigma1, allosteric receptor–receptor interactions in sigma1–D2 and A2A–D2–sigma1 heteroreceptor complexes: role in brain plasticity and cocaine actions
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The field of dopamine D2 receptors and cocaine addiction changed markedly with the discovery of many types of D2 heteroreceptor complexes. We report the existence of D2R–D2R, A2AR–A2AR and sigma1R–sigma1R homoreceptor and A2AR–D2R, D2R–sigma1R and A2AR–D2R–sigma1R heteroreceptor complexes in subcortical limbic areas as well as the dorsal striatum, with different distribution patterns using the in situ proximity ligation assay. These heteromers were demonstrated also through BRET in HEK 293 cells. Antagonistic A2AR–D2R-like receptor–receptor interactions in heteroreceptor complexes in the rat ventral striatum play a role in cocaine addictive behaviors and are differentially affected by cocaine self-administration versus those in the dorsal striatum. More specifically, the activation of the A2AR protomer of this ventral striatal heteroreceptor complex inhibits the development and maintenance of cocaine addictive behavior through inhibition of the D2R protomer recognition and Goα mediated signaling. The anti-cocaine actions of A2AR agonists may involve the restoration of the balance of signaling in the A2AR and D2 homoreceptor complexes and of their integrated signaling in the striatal A2AR–D2 heteroreceptor complexes and increased inhibitory allosteric modulation. Sigma1–D2: Saturation binding assay demonstrated that in membrane preparations of HEK 293 D2R–sigma1R cells, cocaine (1 nM) significantly increased the D2R Bmax values (998 ± 40 fmol/mg protein) over D2R-alone cells (664 ± 37 fmol/mg protein). CREB reporter luc-gene assay indicated that the presence of sigma1R significantly reduced the potency of the D2R-like agonist quinpirole to inhibit the forskolin-induced increase of the CREB signal (antagonistic allosteric receptor–receptor interaction). In contrast, the presence of a low concentration of cocaine (100 nM) was found to markedly increase the quinpirole potency to inhibit the forskolin induced increase of the CREB signal in the D2R–sigma1R cells (synergistic allosteric receptor–receptor interaction). These dual conformational changes induced by cocaine in the D2R–sigma1R heteroreceptor complexes may be associated to enhanced allosteric interactions and a redistribution of both protomers from the intracellular compartment to the plasma membrane. Overall, a potential functional role of the balance between the homoreceptor and heteroreceptor complexes is presented to regulate the integration of multiple signals, specifically in relation to cocaine use disorder.

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