Novel drug pharmacology for targeting dopamine signaling in the brain through ghrelin and dopamine receptor heterodimers

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A major challenge in the field of G-protein coupled receptor (GPCR) drug discovery in CNS is developing specific drugs without side effects. Selection of a drug candidate is traditionally based on canonical signal transduction pathways after expression of the individual GPCRs in heterologous cell lines. However, these assays do not predict the response of target cells in the native tissue; therefore, the desired clinical outcome is often not met. For example, drugs designed for dopamine (DA) receptor subtypes act on all neurons expressing this subtype, but selectivity requires a knowledge of a specific target that discriminates between neuronal subtypes. In neurons, the targeted GPCR is frequently not present in isolation, but with other GPCRs. Some GPCRs are capable of forming heterodimers with a specific GPCR partner resulting in cell and tissue specific modification of canonical signal transduction. To achieve more selectivity for regulating DA signaling, our research focused on regulating DA signaling by target neurons that express dopamine receptor (D1R or D2R) and ghrelin receptor (GHSR1a) heterodimers. We exploit the novel concept that in GPCR heterodimers a neutral antagonist of one protomer can modify the function of the partner protomer by an allosteric mechanism. We detected that D2R:GHSR1a and D1R:GHSR1a heterodimers exist in neurons of native brain tissue resulting in allosteric modification of DA signaling. Our results show that dopamine receptor heterodimers in hypothalamus can regulate food intake in animals through D2R:GHSR1a (Kern et al. (2012), Neuron). We found that in hippocampus D1R:GHSR1a heterodimers regulate DA-dependent memory performance (Kern et al, (2015) Cell). We show DA signaling through these heterodimers is modulated by a GHSR1a antagonist. Hence, treatment with a GHSR1a antagonist provides a selective way of blocking or enhancing DA signaling in neurons expressing the heterodimers without affecting signaling in neurons expressing D1R or D2R alone. These results show potential opportunities for developing more selective therapeutic agents for treating psychiatric disorders involving abnormal DA signaling.