Neuron-selective deletion of β-arrestin-2 uncovers unique mechanism of dopamine D₂ receptor-biased ligands
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The dopamine D₂ receptors (D₂R), which are members of the large G protein-coupled receptor (GPCR) family, are the main target of clinically effective antipsychotics. Although GPCR pharmacology affords selectivity of action, current antipsychotics do not adequately correct the postulated cortical hypodopaminergia and striatal hyperdopaminergia in schizophrenia. The recent observation that GPCRs can signal not only through G proteins but also through the ability of the β-arrestin components of the desensitization machinery to scaffold distinct intracellular signaling complexes provides an opportunity to develop more effective therapies with fewer side effects. Accordingly, a β-arrestin-2 (βarr2)-biased D₂R ligand, UNC9994A, based on the scaffold of aripiprazole was developed [1]. UNC9994A is a partial agonist at βarr2–D₂R interaction but virtually devoid of antagonism at the D₂R–G protein signaling. Using neuron-specific (βarr2)-knockout mice we show that the antipsychotic-like effects of the UNC9994 tool compound in the amphetamine or phencyclidine (PCP) mouse models of psychotic-like behaviors, are driven through antagonism of D₂R–βarr2 interactions in the striatum but agonism of D₂R/βarr2 in the prefrontal cortex. Interestingly, similar to quinpirole, local injection of UNC9994A in the prefrontal cortex inhibits PCP-induced responses and that effect is blocked by inhibition of the GPCR kinase 2 (GRK-2). This paradoxical cortical D₂R/βarr2 agonism can be attributed to elevated cortical expression of βarr2 and GRK-2 compared to striatum. Direct electrophysiological corroboration of the agonist vs. antagonist role of UNC9994A in the prefrontal cortex vs. striatum provides further credence to the in vivo behavioral pharmacological profile of this antipsychotic-like tool compound. Therefore, βarr2-biased D₂R ligands like UNC9994A that exert region-selective actions based on the neuronal complement of βarr2/GRK-2, could possibly provide a path to develop better therapies, which correct both cortical and striatal dopamine dysfunctions.

Reference

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