Abstract View

CHARACTERIZATION OF THE N27 DOPAMINERGIC CELL LINE AS A POTENTIAL MODEL FOR ELUCIDATING THE MECHANISMS OF ACTION OF FUNCTIONALLY SELECTIVE DOPAMINERGIC LIGANDS

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There have been many examples in the literature of GPCR ligands that differentially activate signaling pathways associated with a single receptor ("functional selectivity"). While heuristically useful, many of these studies have been carried out in non-neuronal cell models in which physiological relevance is unclear. Our lab has explored the dopamine D_2 receptor-mediated functional profiles of a number of functionally selectivity ligands. Most of the observations, however, have been made in non-dopaminergic lines (e.g. CHO-K1 and HEK293 cell lines) that were transfected with the D_2 receptor. 1RB3AN27 (N27) cells are from an immortalized line derived from the rat mesencephalon, and may be more physiologically-relevant to functional selectivity of D_2 receptors on dopamine neurons. N27 cells express both tyrosine hydroxylase and the dopamine transporter, and produce measurable amounts of dopamine. Little is known, however, about expression of either endogenous receptors or effector machinery associated with GPCR signal transduction. Using microarray analysis and radioligand-based saturation isotherms, we have determined that these cells do not express significant levels of D_1-like or D_2-like receptors, consistent with prior data using indirect methods. Conversely, many inhibitory heterotrimeric G protein subtypes are expressed. We then stably transfected the human D_{2L} receptor into the N27 cell line, and compared the D_2 receptor-mediated functional characteristics of aripiprazole, dihydrexidine and dinapsoline with the effects of these drugs in CHO cells. Preliminary results suggest that this line can differentiate functionally selective D_2 receptor ligands from typical agonists. These data illustrate that studies in the N27-D_{2L} line may offer insight into physiologically relevant mechanisms of drugs that cause atypical in vivo D_2 mediated responses, both behaviorally and neurochemically.

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