Robust coupling of corticotropin-releasing factor type 1 (CRF_1) and 2a ($CRF_{2(a)}$) receptors to G_s and G_q proteins

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The human corticotropin releasing factor (hCRF) receptors CRF_1 and $CRF_{2(a)}$ couple to the G_s protein and stimulate cyclic AMP production. It has been postulated that CRF receptors may also couple to G_q proteins. To test this hypothesis, binding and signaling properties were determined for both receptor subtypes stably expressed in human embryonic kidney 293 (HEK293). CRF receptors were highly expressed and strongly coupled to G_s in this cell line, with $hCRF_{2(a)}$ showing higher ligand binding than the $hCRF_1$ receptor. In cAMP stimulation experiments most of the agonists strongly stimulated cAMP production in the subnanomolar to low nanomolar range. When the calcium mobilization pathway was investigated good signaling was observed in the fluorometric imaging plate reader (FLIPR) assay. In contrast to the binding and cAMP data however, the $hCRF_1$ receptor was found to couple more efficiently (~1.5- to 2-fold better coupling) than the $hCRF_{2(a)}$ receptor. The potency rank orders for calcium and cAMP responses were identical for both receptors, despite a rightward shift of the dose-response curves in the FLIPR. A complete inhibition of calcium signaling of both $hCRF_1$ and $hCRF_{2(a)}$ receptors was observed in the presence of a phospholipase C inhibitor but not by G_s signaling and calcium channel inhibitors. These data clearly show that CRF receptors besides coupling to G_s can also couple to G_q proteins, thereby activating the Phospholipase C and calcium pathway.

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