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Editorial

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Diseased G Protein-coupled Receptors

One of the exciting scientific developments of the past few years has been the elucidation of a number of features of the structure, function, and regulation of the remarkable superfamily of G protein–coupled receptors (1). The diversity of their functional roles is dazzling and includes signaling by peptides, neurotransmitters (biogenic amines, acetylcholine, etc.), lipids, chemoattractants, sensory stimuli, and cytokines. Many of the structural features of the receptors are well established. The characteristic seven transmembrane-spanning domains form the ligand binding site, while the hydrophilic intracellular loops and carboxy-terminal cytoplasmic tail contain sites of interaction with G proteins and are often studded with phosphorylation sites for kinases, which regulate receptor function (1).

It might be expected that abnormalities of these proteins would wreak very specific forms of pathophysiological havoc. In this issue of *The Journal,* Tsigos et al. (2) demonstrate that a youngster with a rare autosomal recessive disorder, isolated glucocorticoid deficiency (IGD), has inherited two different mutations in the gene for the ACTH receptor (2). The paternal allele contains a point mutation that substitutes a positively charged arginine for neutral serine in the third membrane span, while the maternal allele encodes a receptor truncated early in the third cytoplasmic loop. The authors speculate that the first mutation may alter the ligand binding site of the receptor while the second leads to a nonfunctional receptor. Supporting these contentions, it was found that both heterozygote parents had abnormal ovine corticotropin releasing hormone tests suggestive of subclinical resistance to ACTH. Clark et al. (3) have identified, in another family, a mutation in the ACTH receptor in IGD, a substitution of isoleucine for serine in transmembrane domain 2.

IGD is the second disease in which hormone resistance has been shown to be due to defects in a G protein–coupled receptor. Previously, nephrogenic diabetes insipidus was shown to result from mutations in the gene for the V2 vasopressin receptor (4, and references therein). In this case, a mutant receptor has been expressed and shown to be defective in signal transduction rather than in hormone binding (4). Similar analysis should be performed for these ACTH receptor mutants.

Numerous further examples of alterations in G protein–coupled receptors causing diseases likely will be found. What mechanisms might be involved? Perhaps the most obvious is disruption of receptor signaling, as shown now for ACTH and vasopressin receptors. One can envisage alterations that disturb either ligand binding or G protein coupling. Structural abnormalities of the receptor might also prevent its functional expression at the cell surface or lead to its intracellular accumulation, as is the case with numerous rhodopsin mutations that cause retinitis pigmentosa (5).

Point mutations have also been shown to lead to constitutive activation of receptors, i.e., the receptor shows activity in the absence of ligand (6). Such mutations could cause various forms of cellular hyperfunction or even damage cells by their overactivity. Thus, a constitutively active mutation of rhodopsin leads to retinal degeneration (5).

Several G protein–coupled receptors are mitogenic and capable of transforming cells in vitro when agonist is present. When such receptors are activated by mutations (in the third cytoplasmic loop) they transform cells in an agonist-independent fashion (i.e., they function as oncogenes) (7). Thus, this mechanism could also lead, in appropriate contexts, to tumors of various tissues. Mutations that eliminate key sites of regulation (e.g., phosphorylation sites) might also lead to changes in receptor functions.

Receptor mutations need not lead to disease states but might also underly phenotypic variations within a population. For example, the mouse coat color extension locus has been identified with the MSH receptor gene. A truncated MSH receptor leads to light coat color, while activating mutations of the receptor lead to dark coat color (8). A single amino acid polymorphism in the human red iodopsin gene is responsible for variation in spectral sensitivity to red light (9). Given the recent pace of progress in this field many more such discoveries will likely be forth coming in the near future.

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