The calcitonin gene-related peptide (CGRP) receptor is a family B GPCR. It consists of a G protein-coupled receptor (GPCR), calcitonin receptor-like receptor (CLR) and an accessory protein, receptor activity modifying protein 1 (RAMP1). RAMP1 is needed for CGRP binding and also cell-surface expression of CLR. CLR is an example of a family B GPCR. Unlike family A GPCRs, little is known of how these receptors are activated by their endogenous ligands. This talk considers what is known about activation of family B GPCRs and then considers how this might be applied to CLR, particularly in the light of new knowledge about the crystal structures of family A GPCRs. Mutagenesis, bioinformatic and modelling data will be presented which suggests the location of key switches involved in the activation of the family B GPCRs and what represent the family B equivalent of the DRY and NPXXY motifs found in family A GPCRs.