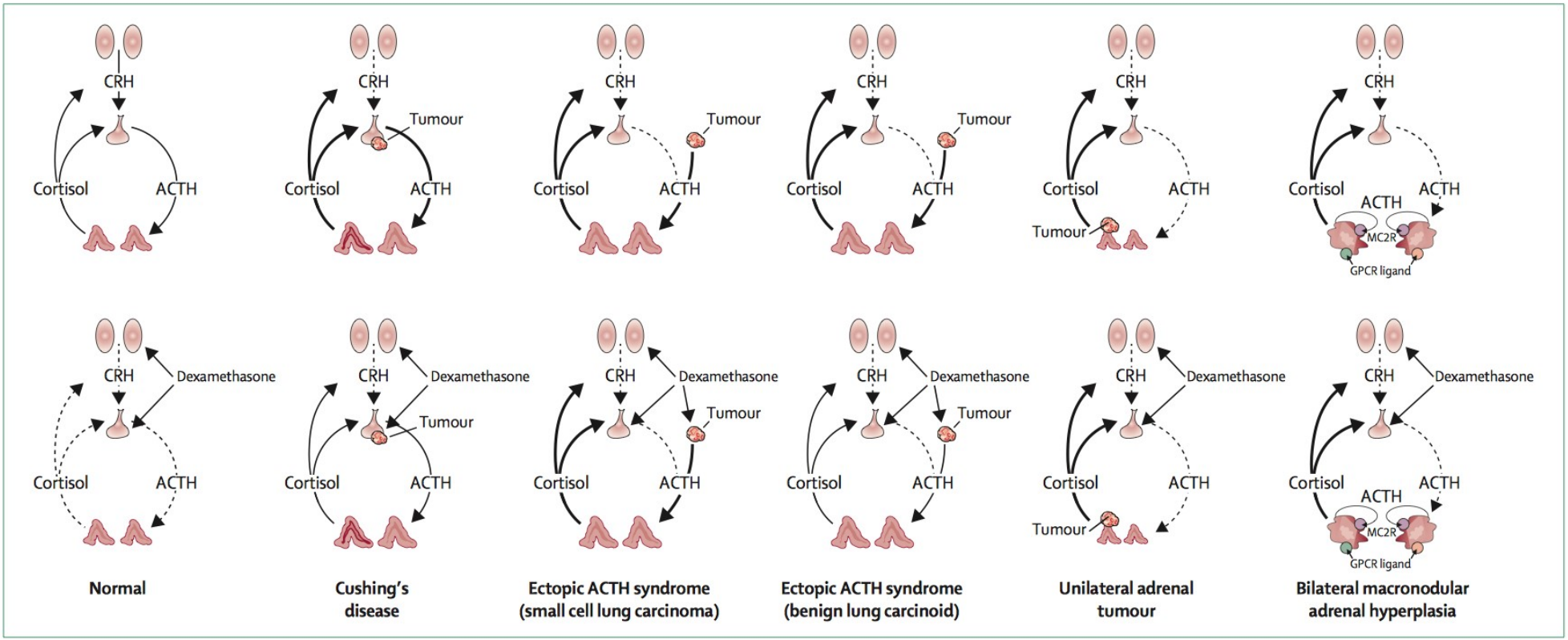

Figure 2: **Differential regulation of the hypothalamic-pituitary-adrenal axis in healthy individuals and in the various causes of Cushing's syndrome**
In healthy people, stimulation of the hypothalamus by CNS centres regulates the secretion of CRH, which in turn increases ACTH secretion. ACTH stimulates adrenal secretion of cortisol, which, like exogenous low dose dexamethasone (lower panel), inhibits the secretion of both CRH and ACTH. In Cushing's disease, excess ACTH originating from the corticotroph tumour is partly resistant to excess glucocorticoid and high dose dexamethasone suppression, while CRH and healthy corticotropes are suppressed. Ectopic ACTH secretion from malignant tumours is usually autonomous from CRH and dexamethasone regulation, whereas ectopic ACTH originating from up to 50% of benign neuroendocrine tumours can be suppressed partly by high dose dexamethasone or respond to exogenous CRH or desmopressin, similar to Cushing's disease. In adrenal Cushing's syndrome caused by unilateral adrenal tumours, ACTH is suppressed by excess cortisol and is not modified by CRH or high doses of dexamethasone. In bilateral macronodular adrenal hyperplasia, cortisol can be regulated by the ligands of various aberrant hormone receptors (GPCR) stimulating paracrine ACTH production by adrenal hyperplasia cells acting on the ACTH receptor (MC2R); however, circulating ACTH concentrations are still low. Normal hormone secretion is shown by lines, suppressed secretion by thinner or dotted lines, and hypersecretion by thick lines. Modified from reference 169 by permission of Massachusetts Medical Society. ACTH=adrenocorticotropic hormone. CRH=corticotropin-releasing hormone. GPCR=G-protein-coupled receptor. MC2R=melanocortin 2 receptor.