G-Protein-Coupled Receptors

R.D. Sanders, D. Brian, and M. Maze(*)

Abstract  G-Protein-coupled receptors mediate many of the hypnotic and analgesic actions of the drugs employed in anesthesia. Notably, opioid agonists represent the most successful and efficacious class of analgesic agents employed over the last century. Also, major clinical advances have been made by the study of \( \alpha_2 \) adrenoceptor agonists, which possess both hypnotic and analgesic qualities that are being increasingly exploited in both anesthetic and critical care settings. Furthermore
orexin, γ-aminobutyric acid (GABA), and muscarinic cholinergic receptors have been identified as potential anesthetic targets; clinical exploitation of ligands at these receptors may lead to important advances in anesthetic pharmacology. In this review we discuss the relevant molecular and neural network pharmacology of anesthetic agents acting at G-protein-coupled receptors.

1 Introduction

Guanine nucleotide-binding protein (G-protein)-coupled receptors (GPCRs) are the largest and most versatile group of cell surface receptors, and represent a conserved mechanism for extracellular signal perception in eukaryotic organisms (Pierce et al. 2002). Various stimuli (e.g., photons and odors) and ligands (e.g., neurotransmitters, cytokines, hormones, and drugs) can activate intracellular signaling cascades via G-proteins. Indeed, GPCRs mediate many anesthetic and analgesics effects of the drugs we employ.

1.1 Structure of G-Protein-Coupled Receptors

GPCRs are a superfamily of integral membrane proteins, and possess seven transmembrane helices (I–VII), three extracellular loops (II–III, IV–V, and VI–VII), and three cytosolic loops (I–II, III–IV, and V–VI). They have a periplasmic N-terminal domain (N), and a cytosolic C-terminal (C) domain; domain VIII is also contained in the C-terminal and runs parallel to the cytosolic membrane surface (Palczewski et al. 2000; see Fig. 1). Signal transduction through membrane-bound GPCRs enables diverse intracellular responses to a wide array of chemical ligands in a highly selective fashion. To date, 616 functionally diverse members (2.3% of total genes) have been described (Hemmings and Girault 2004), facilitated by a shift from ligand-based to sequence-based discovery (Lee et al. 2001). Perhaps surprisingly, current evidence suggests that of all drugs targeting GPCRs, the majority exert their effect predominantly on a group of only approximately 30 of these (Wise et al. 2004).

1.2 G-Protein-Coupled Receptor Subtypes

In 1971, Rodbell first outlined how a guanine-nucleotide binding regulatory protein linked receptors with downstream cellular effectors, in the context of hormonal modulation of the adenylyl cyclase system (Rodbell et al. 1971). Subsequent purification led to the identification of a heterotrimeric G-protein, composed of α-, β-, and γ-subunits, and molecular cloning has now defined 35 genes encoding