GABA<sub>B</sub> Receptor as a Potential Therapeutic Target

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Summary

At present, the only therapeutic agent in current use that is known to exert its effects through the GABA-B receptor is baclofen, the β-chlorophenyl analog of GABA. This compound is used extensively as a centrally active muscle relaxant, but it has been shown clinically to exert additional effects, including analgesia, suppression of drug addiction, and cessation of chronic cough. Basic research indicates that there may be many other applications not only for agonists, but also antagonists at the GABA-B receptor, and this chapter seeks to examine the potential significance of these and also of allosteric modulators for the receptor, which have been recognized during the past 5 yr. GABA-B receptors have been implicated in neuronal processing in many brain regions and there is considerable evidence for their pathological involvement in various diseases of the central nervous system, such as absence epilepsy, depression, and even in the etiology of nicotine dependency in humans. Novel chemical entities will surely be the key to exploiting this receptor. At present, the only agonist (baclofen) in the clinic frequently produces unwanted side effects, and this clearly limits its usage. There are no antagonists in clinical therapy, although trials for cognition deficits are underway. Metabotropic receptors, of which the GABA-B receptor is a member, provide most of the targets for our currently used therapeutic agents; thus, there seems to be every reason to believe that the rewards for discovering clinically available GABA-B receptor ligands could be high.

Key Words: GABA<sub>B</sub> receptor; G protein; therapeutic target; nociception; cognition; addiction; epilepsy; depression and anxiety.
1. Introduction

In preceding chapters details of the heterodimeric structure of the receptor have been presented and whereas each of the two subunits that make up the receptor might contribute independently to the function of the receptor, the dimer is the form on which the receptor pharmacology is based (8). The two receptor subunits, γ-aminobutyric acid (GABA$_{B1}$) and GABA$_{B2}$, which provide different functions are mutually dependent on each other. The former contains the GABA-binding domain (9–12), whereas GABA$_{B2}$ provides the G protein coupling mechanism and also incorporates an allosteric modulatory site within its heptahelical structure (13–15). Whereas different functional isoforms of at least GABA$_{B1}$ have been defined (16–22) there is, as yet, no unequivocal evidence for distinct GABA$_{B}$-receptor subtypes (8).

The overall distribution of the receptor in the brain has been delineated using autoradiographical techniques with neurochemical and electrophysiological studies revealing both pre- and postsynaptic locations where they are coupled to Ca$^{2+}$ and K$^+$ channels, respectively. When receptor activation occurs, not surprisingly, a variety of effects can arise as a consequence of inhibition of transmitter release and/or postsynaptic neuronal hyperpolarization. Having a selective agonist for the receptor together with information derived from “knockout” mice which exhibit hyperalgesia, seizures, hyperlocomotion, impaired learning, loss of responses to baclofen, and lack of GABA$_{B}$-binding sites throughout the brain (23–26), has provided the basis for much of the speculation about the potential therapeutic benefits of both agonists and antagonists for the receptor. A list of some of the actions of baclofen (in vitro and in vivo) is shown in table 1 and predominant among the in vivo effects are the muscle relaxant, antinociceptive, and antidrug craving effects as well as the reduction in cognitive behavior that have been reported.

2. Mechanisms Associated With the GABA$_{B}$-Receptor Activation

Both biochemical and ion channel events have been linked to GABA$_{B}$-receptor activation (8). The common feature of these events is the coupling to G proteins (27,28) but the channel events appear not to be dependent on modifications in the generation of cyclic adenosine monophosphate, which occur as a consequence of G protein coupling to adenylyl cyclase (29–32). Instead there would seem to be a direct influence of the G protein on the ion channels. The events that occur following agonist binding to the receptor domain, which is located only in the GABA$_{B1}$-subunit, are mediated by the GABA$_{B2}$-subunit and it is in this subunit within the heptahelical domain where an allosteric receptor modulatory site is also located.