GABA-drug interactions

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1 Introduction ................................................ 224
2 The GABA receptor-chloride channel complex .......................... 224
3 The picrotoxinin/convulsant receptor .................................. 227
4 The benzodiazepine receptor ............................................ 228
5 The barbiturate receptor ................................................ 233
Acknowledgment ................................................................ 237
References ........................................................................ 238
Introduction

γ-Aminobutyric acid is the major inhibitory neurotransmitter in the central nervous system and is widely utilized in virtually all anatomic regions of the brain and spinal cord [1, 2]. In recent years, pharmacological evidence at all levels (organismal, tissue, cellular, and molecular) have implicated GABA in a variety of human clinical problems and, correspondingly, in the action of numerous drugs showing general excitatory or depressant action on the central nervous system [3–5]. These include convulsants like picrotoxin [6], bicuculline [7], cage convulsants [8], pentylenetetrazol [9], and convulsant benzodiazepines [10, 11], as well as depressants like benzodiazepines (used for anxiolytic, anticonvulsant, sedative-hypnotic, or muscle relaxant activity [12], barbiturates (used today as anticonvulsants and general anesthetics, and formerly as sedative-hypnotics [13]), other general anesthetics [14, 15], including ethanol [16, 17], and a variety of related substances [18]. Because of the widespread function of GABA in the brain, interactions with virtually all neuropharmacological agents and other neurotransmitters have been described. However, increasing bodies of evidence suggest that the drugs mentioned above act by modifying the postsynaptic response to GABA directly at the GABA receptor-chloride ion channel complex [19, 20]. This review will therefore be limited to agents of this type (an amazingly large number) that have receptor sites on the GABA receptor complex. This GABA receptor is defined not only by the chloride channel effector, but also by sensitivity to the agonist muscimol and the antagonist bicuculline, to distinguish it from other less widespread GABA receptors, such as baclofen-sensitive subtype [2, 5]. The former is sometimes called GABA_A, the latter GABA_B receptors. We shall refer to the GABA_A type as simply GABA receptors.

The GABA receptor-chloride channel complex

Inhibitory synaptic transmission mediated by GABA is most often produced by a rapid increase in chloride permeability of the postsynaptic cell membrane [1–5]. By analogy with the nicotinic acetylcholine receptor of the neuromuscular junction [21], the peptides making up the GABA recognition protein (receptor) are thought to also form the structural walls of the transmembrane ion channel, whose opening