Selective Actions on Sleep or Anxiety by Exploiting GABA-A/Benzodiazepine Receptor Subtypes

Stephen M. Stahl, M.D., Ph.D.

Issue: *New drugs that selectively target subtypes of the GABA-A/benzodiazepine receptor complex may have anxiolytic actions without sedative hypnotic or amnestic actions.*

Comeback Agents?

Are agents that act at benzodiazepine receptors making a comeback as anxiolytics? Benzodiazepines, once the most widely prescribed of all drugs, are still used to treat anxiety. All currently marketed benzodiazepines share rapid onset of sedative-hypnotic, anxiolytic, anticonvulsant, and muscle relaxant properties.[1] Choice of agent for each of these indications is largely a function of differential half-lives and marketing considerations rather than a consequence of any real selectivity of therapeutic action. Because of their tendency to produce drug dependence, amnestic effects, and sedation, benzodiazepines have fallen out of favor as first-line treatments for anxiety disorders. The antidepressants that have largely replaced benzodiazepines as anxiolytics, however, are not particularly rapid in onset and have their own side effect profiles. Thus, there is the lingering desire for a rapid-acting anxiolytic that lacks the undesirable side effects of the benzodiazepines. Recent advances in the molecular biology of benzodiazepine-sensitive gamma aminobutyric acid-A (GABA-A) receptors suggest that it may be possible to target benzodiazepine receptors with novel agents that retain the anxiolytic actions but not the undesirable actions of the classical benzodiazepines.[2,3]

Pieces of the Puzzle

It is now known that many different subtypes of GABA-A receptors exist, based on the fact that many different subunits can go into assembling GABA-A receptors. Every fully constituted GABA-A receptor is a pentameric puzzle.[1–3] The whole receptor puzzle is organized as 5 proteins surrounding a central chloride channel (Figure 1), analogous to the structure of nicotinic cholinergic receptors.[4,5] For GABA-A receptors, 3 different puzzle pieces, known as subunits, fit together to make up each protein. More than a dozen subunits have already been characterized and are the secret to the differences among various GABA-A receptors.

Most often one α, one β, and one γ subunit are pieced together to form one of the pentameric proteins (Figure 1). The β_3 subunit is present in most areas of the brain. If a γ_2 subunit fits together with any one of several α subunits, the interface forms a benzodiazepine receptor. GABA itself binds to another site on the fully assembled receptor protein. Some of the most important distinctions among various GABA-A receptors depend on which α subunit they contain. The best characterized of the GABA-A receptors include those with α_1, α_2, or α_3 subunits.[2,3]

GABA-A receptors with α_1 subunits may mediate sedative hypnotic actions and perhaps amnesia. Those with α_2 subunits probably mediate anxiolytic actions. They are located mainly in limbic areas such as hippocampus, cerebral cortex, and striatum. GABA-A receptors with α_3 subunits may regulate various neurotransmitters, since they are located in the serotonin and norepinephrine neurons of the brainstem reticular formation, in basal forebrain cholinergic neurons, and in GABA neurons in the reticular nucleus of the thalamus.

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From the Neuroscience Education Institute in Carlsbad, Calif., and the Department of Psychiatry at the University of California San Diego.

Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Editor, BRAINSTORMS, Neuroscience Education Institute, 5857 Owens Street, Ste. 102, Carlsbad, CA 92009.

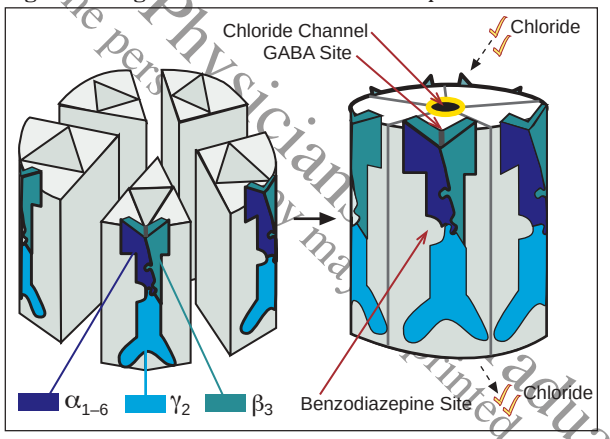
Take-Home Points

- GABA-A receptors have binding sites for the neurotransmitter GABA as well as for benzodiazepines.
- Different subunits of benzodiazepine-sensitive GABA-A receptors combine to form a variety of receptor subtypes that are distributed in unique brain regions and mediate distinct functions.
- Drugs that selectively target GABA-A receptor subtypes could lead to a new generation of anxiolytics that lack the sedation, amnesia, and dependence of the current benzodiazepines.

Drugs That Target GABA-A Receptor Subtypes Selectively

All classical benzodiazepines appear to act indiscriminately at each of the GABA-A α subtypes, which is the reason they have not only anxiolytic properties but also sedative-hypnotic, amnestic, and anticonvulsant properties. Several newer drugs, on the other hand, may activate only some of the GABA-A α subtypes. For example, 2 of the newest sedative-hypnotics, zolpidem and zaleplon, which are not benzodiazepines, bind somewhat selectively to the α_1 subtype of the GABA-A receptor.[2,3] Several other drugs still in development appear to have anxiolytic but not sedative-hypnotic actions in animal models. They all activate the α_2 subtype of GABA-A, some quite selectively (e.g., agents like pagoclone; CP615,003 or NGD91,3; SL651,498; and L-838,417).[2,3]

Figure 1. Organization of a GABA-A Receptor[a]



[a]On the left is shown each of the 5 proteins that combine to form a fully constituted receptor complex with a chloride channel in the middle. It can also be seen that each protein has 3 subunits. Variations of the α subunit are associated with unique functions and anatomical distributions. Each protein has a binding site not only for GABA but also for benzodiazepines.

GABA Stabilizers and Partial Agonists

Selective activation of the right GABA-A receptor to produce anxiolytic effects without sedation and amnesia is only part of the story. It is also highly desirable for new anxiolytics not to cause dependence. The best candidate may be a partial agonist, and not a full agonist, at α_2 GABA-A receptors. Partial agonists, like the new dopamine system stabilizers, such as aripiprazole,[6,7] can stabilize neurotransmitter systems.

Classical benzodiazepines are full agonists, causing adaptation of GABA-A receptors following chronic treatment, with resultant benzodiazepine dependence and withdrawal effects. It may be possible to find a partial agonist with the ability to activate α_2 GABA-A receptors sufficiently so that anxiety is reduced, but not so powerfully that the receptors adapt and develop dependence. Thus, the new subtype-selective agents of the future may also be partial agonists, or GABA stabilizers.

Summary

The next generation of anxiolytics may be subtype-selective partial agonists at GABA-A receptors. By exploiting new psychopharmacologic principles, such as the targeting of receptor subtypes that have unique subunits and the partial activation of these subtypes with stabilizers, we may eventually have anxiolytics that are rapid acting, but without sedation, amnesia, or dependence.

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