New Insights into the $GABA_A$ Receptor

By Nancy A. Ator, PhD, and Una D. McCann, MD

The ability of γ-aminobutyric acid (GABA) to decrease electrical activity in brain was discovered in the mid-1950s. In the 1960s its role as the major inhibitory neurotransmitter in the mammalian central nervous system was delineated. Progress in delineating the structure of the first-studied GABA receptor, GABA type A ($GABA_A$), did not occur until ~20 years later.[1] Recognition of the role of GABAergic transmission in the actions of major drug classes occurred well after their introduction into clinical practice. A report on GABA pharmacology "emphasized that the GABA receptor has not yet been well defined" but "an association between GABA and benzodiazepines [BZs] appears evident."[2] In fact, the explanatory focus for BZ therapeutic effects was on a BZ "receptor," probably two.[3]

BZs appeared in clinical practice in he 1960w with the release of chlordiazepoxide and found wide physician acceptance. Along with their rather unique efficacy in anxiolysis, BZs have important anticonvulsant, hypnotic, muscle relaxant, and amnestic effects useful in the context of surgery. Their excellent safety in overdose was a tremendous advance for outpatient use. Unwanted effects of daytime sedation, undue muscle relaxation in treatment of anxiety, and of "hangover" with some BZs used for sleep disorders were minor inconveniences compared with the problems of other drug treatments available at that time. Physical dependence emerged as an unwanted "side effect" of repeated BZ administration and psychological dependence manifested in extreme reluctance of patients to be tapered off BZs. In 1975, legal scheduling of the then-marketed BZs in the United States brought restrictions on prescribing.

First-line use of BZs for chronic treatment of anxiety gave way to reliance on other types of drugs and other therapeutic methods. Anxiety disorders frequently occur comorbid with affective disorders, making the use of antidepressants efficient. Empirical research demonstrated the efficacy of nonpharmacological approaches, such as cognitive-behavioral therapy (CBT), for the treatment of anxiety disorders. Some evidence suggested that concomitant use of a BZ decreases the efficacy of CBT. However, patient acceptance of BZs and their safety still made them attractive.

The evidence for heterogeneity of BZ receptors prompted the idea that pharmacotherapy for anxiety could preserve the anxiolytic efficacy of the BZs but eliminate unwanted effects might be attainable. In the early 1980s, the quest for a nonsedating, non-dependence-producing BZ began as well as diversification in clinical approaches to the treatment of anxiety. By the late 1980s, we learned there was much more than heterogeneity in BZ binding sites to BZ neuropharmacology. Studies of the molecular pharmacology of GABA neurotransmission revealed that four of a possible multitude of $GABA_A$ subtypes contain BZ binding sites.[4] Chemistry focused on making compounds selective for BZ/$GABA_A$ subtypes has been motivated by the goal of discovery of a distinctly targeted treatment for anxiety with less baggage for the prescriber and patient than classic BZs. This quest is providing exciting opportunities for learning more about the molecular biology of behavior itself.

Gerard R. Dawson, PhD, and colleagues introduce the structure of the $GABA_A$ receptor and its subtypes by reviewing research on mutant mice and $GABA_A$ subtype-selective compounds to understand subtype-specific mediation of the classic BZ behavioral profile. Insight into mediation of the BZ amnestic effect is yielding understanding of its mechanism, which, in turn, suggests a route to developing a cognitive enhancer.

Nancy A. Ator, PhD, addresses abuse liability and dependence potential of treatments for anxiety and sleep disorders by reviewing the process by which new centrally acting drugs are evaluated for decision making on legal scheduling and the behavioral, laboratory-based components of abuse liability evaluations. Preclinical data for new $GABA_A$ subtype-selective agonists and partial agonists are compared with the profiles for classically used anxiolytics and hypnotics. Results suggest the reality of separating anxiolytic effect from those suggestive of abuse liability and the nature of subtype mediation of BZ subjective effects.

James K. Rowlett, PhD, and colleagues review the concept of antagonism at the BZ binding site, when binding has little or no intrinsic efficacy. They report on a novel $GABA_A$ subtype-selective BZ antagonist and its usefulness for delineating subtype-specific mediation of BZ agonism. Preclinical data are followed by discussion of important clinical applications of BZ antagonists.

David J. Nutt, MD, PhD, reviews categories of anxiety disorders and pharmacologic approaches to treatment, discussing the predominance of antidepressants and other non-GABAergic drugs in the treatment of these disorders in the context of the concerns regarding BZ prescription. Clinical uses of BZs are described, including in conjunction with a drugs other classes. The major concern for BZ abuse and dependence has limited long-term therapeutic use of these compounds and the advent of BZ ligands free of these liabilities is welcomed. CNS

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