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Editorial

Six decades of GABA

While it had been known for some time that γ-aminobutyric acid (GABA) is present in biological tissue, it wasn't until 1950 that Roberts, Frankel and Udenfriend first positively identified large quantities of this amino acid in mammalian brain. The Roberts report also provided evidence that GABA is formed from glutamic acid in brain, and contained speculation that this conversion takes place by α-decarboxylation. Thus, the dawning of the 21st century ushered in the 6th decade of research aimed at exploiting this finding. This special issue of *Biochemical Pharmacology* consists entirely of articles written by some of the leading investigators in the field to celebrate the impact of this discovery on defining mechanisms underlying mammalian neurotransmission and on the therapeutic management of neurological and psychiatric disorders.

The neurotransmitter properties of GABA were first characterized in crustaceans by Fatt, Katz, Kuffler, Kravitz, Otsuka, Okada, Takeuchi and others. However, it wasn't until the late 1960s that Krnjević and Schwartz demonstrated convincingly that GABA mimics the action of an endogenous neurotransmitter in mammalian brain. This conclusion was reinforced by the biochemical and pharmacological studies of Roberts and Kuriyama, as well as Iversen, Mitchell, Kelly, and Neal in the United Kingdom, Johnston, Curtis, and Beart in Australia, Ito and Obata in Japan, among others. The results revealed that GABA is synthesized, stored, released, and accumulated by mammalian neurons, thereby displaying the hallmarks of a classical neurotransmitter. Bloom and Iversen demonstrated that GABA is stored in more than 30% of central nervous system neurons, suggesting an important role in regulating overall nervous system function.

Because the hyperpolarizing response to GABA is observed throughout the central nervous system, questions lingered about the specificity of its action. This issue was settled by Johnson, Curtis and their colleagues when they found that bicuculline, a convulsant alkaloid, selectively blocks the inhibitory response to GABA, suggesting the existence of a pharmacologically and molecularly distinct receptor. This discovery encouraged medicinal chemistry efforts by Krogsgaard-Larsen, Schousboe and others to design, synthesize and test the GABA receptor agonists, antagonists and uptake inhibitors necessary to further characterize this system. The development in the mid-1970s by Enna and Snyder, as well as Richard W. Olsen and his colleagues, of radioligand binding assays for the GABA receptor provided powerful tools for defining the biochemical and pharmacological properties of this site. This was followed by the reports of Squires, Braestrup, Möhler and Okada of a specific benzodiazepine recognition site on the GABA receptor that, along with the physiological studies of Haefely and his colleagues, demonstrated its involvement in the mechanism of action of this drug class. Subsequent receptor binding work by these investigators, as well as Costa and Guidotti, provided evidence that this ionotropic receptor is regulated allosterically, and mediates the actions of variety of agents, including ethanol and some general anesthetics.

The 1980s witnessed the identification by Bowery and his colleagues of a distinct, baclofen-sensitive, metabotropic GABA receptor that is designated $GABA_B$ to distinguish it from the bicuculline- and benzodiazepine-sensitive, ionotropic receptor now referred to as the $GABA_A$ site. Work by Bowery, Hill, Enna, Karbon and others revealed that the $GABA_B$ receptor plays an important role in mediating coincident signaling in brain. Kerr and Ong prepared phaclofen, the first $GABA_B$ receptor antagonist, making it possible for Nicoll and others to define the physiological properties of these sites. Subsequently, Froestl and his colleagues synthesized and tested a variety of highly selective, potent, and systemically active $GABA_B$ receptor agonists and antagonists that have proven invaluable in characterizing the molecular properties of this site and the therapeutic potential of this drug class.

By the end of the 1980s the genes encoding the $GABA_A$ receptor subunits were cloned, with studies by Richard W. Olsen, Barnard, Sieghart, Möhler and others suggesting this receptor system is represented by a family of molecularly distinct, pentameric structures that possess a number of pharmacologically meaningful sites, each of which can be manipulated to alter receptor sensitivity and function. In the late 1990s the work of Bettler, White, Kaupmann, Jones, Pangalos, Moss, and Pin resulted in the

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cloning of $GABA_B$ genes and the demonstration that this receptor is a heterodimeric metabotropic site.

As detailed in studies and reports by Macdonald, Sloviter, Mody, Coyle and Benes, alterations in $GABA_A$ or $GABA_B$ receptor function contribute to the symptoms of a host of neurological and psychiatric disorders. For example, at least half of the current antiepileptic medications influence GABAergic transmission, and the benzodiazepines have for years been a mainstay in the treatment of epilepsy, anxiety, and insomnia. The work of Castro-Lopes, Enna, Bowery and others has revealed that GABA is involved in the perception of pain. Moreover, Harris, Koob, and Gallagher have shown that the GABAergic system is important in learning and memory, is a component of the brain reward system, plays a critical role in the response to drugs of abuse, such as ethanol and cocaine, and in the development, and possible treatment, of addiction.

A great deal of progress has been made in defining GABA transmission since Roberts first reported on the chemical nature of a ninhydrin-reactive material in brain. This work has also provided new insights into fundamental features of neurotransmission in general, such as the importance of allosterism and coincident signaling in regulating receptor function and overall cellular activity. These studies have led to the design and development of new drugs and potential therapeutic agents. Given the successes achieved over the first 50 years of GABA research, it is certain the 6th decade will yield its share of surprising discoveries and new insights. Published in this issue are articles providing thoughts and perspectives on this topic, some with the benefit of hindsight, others in the context of recent findings, but all with a hint, or prediction, of what the future holds as the secrets of GABA neurotransmission continue to unfold.

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