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Invited review

$GABA_A$ receptor: Positive and negative allosteric modulators

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ABSTRACT

gamma-Aminobutyric acid (GABA)-mediated inhibitory neurotransmission and the gene products involved were discovered during the mid-twentieth century. Historically, myriad existing nervous system drugs act as positive and negative allosteric modulators of these proteins, making GABA a major component of modern neuropharmacology, and suggesting that many potential drugs will be found that share these targets. Although some of these drugs act on proteins involved in synthesis, degradation, and membrane transport of GABA, the GABA receptors Type A ($GABA_AR$) and Type B ($GABA_BR$) are the targets of the great majority of GABAergic drugs. This discovery is due in no small part to Professor Norman Bowery. Whereas the topic of $GABA_BR$ is appropriately emphasized in this special issue, Norman Bowery also made many insights into $GABA_AR$ pharmacology, the topic of this article. $GABA_AR$ are members of the ligand-gated ion channel receptor superfamily, a chloride channel family of a dozen or more heteropentameric subtypes containing 19 possible different subunits. These subtypes show different brain regional and subcellular localization, age-dependent expression, and potential for plastic changes with experience including drug exposure. Not only are $GABA_AR$ the targets of agonist depressants and antagonist convulsants, but most $GABA_AR$ drugs act at other (allosteric) binding sites on the $GABA_AR$ proteins. Some anxiolytic and sedative drugs, like benzodiazepine and related drugs, act on $GABA_AR$ subtype-dependent extracellular domain sites. General anesthetics including alcohols and neurosteroids act at $GABA_AR$ subunit-interface *trans*-membrane sites. Ethanol at high anesthetic doses acts on $GABA_AR$ subtype-dependent *trans*-membrane domain sites. Ethanol at low intoxicating doses acts at $GABA_AR$ subtype-dependent extracellular domain sites. Thus $GABA_AR$ subtypes possess pharmacologically specific receptor binding sites for a large group of different chemical classes of clinically important neuropharmacological agents.

This article is part of the "Special Issue Dedicated to Norman G. Bowery".

Contents

Abbreviations: GABA, γ-aminobutyric acid; GABAAR, GABAA receptors; LGIC, ligand-gated ion channels; PLGIC, pentameric LGIC; CNS, central nervous system; ECD, extracellular domain; TMD, trans-membrane domain; GlyR', glycine receptors; TM1, trans-membrane helix 1; TM2, trans-membrane helix 2; TM3, trans-membrane helix 3; SCAMP, Substituted cysteine modification protection.

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1. Introduction

The concept of receptors as biochemical mediators of cell signaling including the actions of neurotransmitters has existed for over 100 years, coming to an era of respect for receptors' existence with the advent of radioligand binding in the 1960's and '70's, and a major sub-discipline of pharmacology in the birthplace and world center of pharmacology, the United Kingdom (Rang, 1973; Cuatrecasas, 1974). Proteins were established as neurotransmitter receptors, notably for established neurotransmitters like acetylcholine (Changeux, 1981) and catecholamines (Pepeu et al., 1980) and drugs like opiates that turned out to be ligands for receptors of endogenous neurotransmitters (Snyder, 2017). The recognition of amino acids (Curtis and Johnston, 1974) including glutamate (Watkins and Evans, 1981) and γ−aminobutyric acid (GABA)* as major neurotransmitters proceeded during the '60's and 70's (Eccles, 1969), culminating in a meeting organized by Eugene Roberts in 1975 at the Kroc Foundation's Golden Arches Ranch outside Santa Barbara, California, with classic presentations and reviews published by world leaders (Roberts et al., 1976). But the real beginning of the GABA era occurred at a world-wide meeting of virtually all interested parties organized by Frode Fonnum in Spatind, Norway in 1977 (Fonnum, 1978; Dray and Bowery, 1978; Olsen et al., 1978). This was where most of the players who developed the GABA field in subsequent years first gathered and met, including Norman Bowery.

Just beginning work on GABA, I found Norman a pioneer, publishing in the late 70's on $GABA_A$ receptor ($GABA_AR$) positive and negative allosteric modulators (PAMs and NAMs) that will be the emphasis of this chapter. Yes, Norman made many contributions to the GABA field including GABA transporters and $GABA_ARs$ besides $GABA_B$ receptor work! I visited him in London in early 1978 at the School of Pharmacy. Not only did he keep me excited about GABA for an hour, but his whole department of 10 also talked to me only about GABA. I felt it was like heaven, and, considering the outstanding pharmacology community in England, including GABA workers, I hastily arranged a sabbatical leave in London for the following year at the National Institute for Medical Research, Mill Hill, with numerous jovial, valuable visits with Norman.

The excitement of these times (late '70's to early '90's) in neuropharmacology was due to the new clues to understanding the molecular mechanisms of action of signaling systems like neurotransmission, but also neuropharmacological agents important in humans, notably the anxiolytic, anticonvulsant benzodiazepines, picrotoxin-like convulsants, general anesthetics including both volatile agents (like isoflurane), and intravenous agents: barbiturates, etomidate, propofol, as well as long-chain alcohols, including low potency actions of EtOH, plus neuroactive steroids. All are $GABA_AR$ PAMs and NAMs. Furthermore, at another site on $GABA_ARs$, high potency (low mM) EtOH actions are also shown to be due to action as a $GABA_AR$ PAM. Norman Bowery was one of the leaders in recognizing that the field possessed valuable tools in the libraries of chemical compounds that exhibit pharmacological efficacy: these are ligands, not only for the isosteric GABA binding sites on the critical macromolecules (transporters and receptors) (Bradley and Dray, 1973; Bowery, 1984; Tanaka and Bowery, 1996; Ejeberg et al., 2002; Johnston, 2000; Martin and Olsen, 2000; Olsen, 2014; Ticku and Maksay, 1983; Enna, 1984; Bowery et al., 1995), but also ligands for allosteric sites on those same neurotransmission proteins (Haefely et al., 1975; Ticku and Olsen, 1980; Supavilai et al., 1982; Johnston, 1984; Harrison and Simmonds, 1984).

2. GABA and $GABA_AR$

In this special issue for Norman Bowery with emphasis on $GABA_B$ receptors, the importance of GABA in brain function, and the pharmacology, structure and function of $GABA_B$ receptors (Bowery et al., 2002; Pin and Bettler, 2016) will be sufficiently covered. Unlike the $GABA_B$ receptors, which are members of the relatively slow, G-protein-coupled receptors (GPCR) category, $GABA_ARs$ are part of the rapid-acting, ligand-gated ion channel (LGIC) receptor category. They are members of the pentameric (PLGIC) superfamily, which includes nicotinic acetylcholine, $5\text{-}HT_3$, and inhibitory glycine receptors, which differ from the tetrameric ionotropic glutamate receptors and trimeric purinergic subclass of LGIC (Collingridge et al., 2009). The PLGIC superfamily has many structural features in common, including homologous subunit sequences and functional domains within the heteropentameric proteins (Galzi and Changeux, 1994; Harvey and Betz, 2000; Olsen and Sieghart, 2008). Many are understood at the high (atomic) resolution structural level, based on both X-ray crystal structures of model homopentameric proteins (see below), as well as computer-enhanced images generated from electron microscopy (Unwin, 2005) and cryo-electron microscopy, e.g., TRK (Julius, 2013), NMDA (Lu et al., 2017), and the closely related PLGIC glycine receptor (Du et al., 2015). The latter technology could be applied to both the structure of the $GABA_AR$ channel, and location of the functional ligand-binding sites, and the allosteric modulatory sites on native heteromeric membrane proteins, including subtypes, as well as plastic changes occurring in vivo, as in learning and memory, and chronic drug treatment. Other developments are erupting from the use of high resolution proteomics to identify partners for protein−protein interactions, e.g., for $GABA_BRs$ (Schwenk et al., 2016) and $GABA_ARs$ (Yamasaki et al., 2017).

The $GABA_ARs$ are constituted from a family of 19 homologous genes categorized by degree of sequence identity as different subunit families (α1–6, β1–3, γ1–3, δ, ε, θ, π, and ρ1–3). They are usually constructed with 2 copies of an α subunit, 2 copies of a β subunit, and one copy of either a γ subunit, or another such as δ, to form a family of perhaps 2 dozen heteropentameric subtypes, about one dozen of which are sufficiently abundant to have physiological relevance (Barnard et al., 1998; Olsen and Sieghart, 2008). These vary in age and brain regional as well as subcellular distribution, and thus in functional, circuitry involvement, regulatory aspects, and pharmacology, depending on the subunit composition, and involving minor structural heterogeneity within a common basic structure and function. The heterogeneity provide the opportunity for possible subtype-selective pharmacological ligand specificity and clinical therapeutics with minimal side effects (Whiting, 2003; Hevers and Lüddens, 1998; Möhler et al., 2002).

$GABA_ARs$ and $GABA_B$ receptor proteins differ greatly from each other, including the GABA binding site domains, so that the pharmacology of isosteric analogues of GABA are different for the two: muscimol (agonist) and bicuculline (antagonist) are specific