Review

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The Gamma-Aminobutyric Acid B Receptor in Depression and Reward

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ABSTRACT

The metabotropic gamma-aminobutyric acid B ($GABA_B$) receptor was the first described obligate G protein–coupled receptor heterodimer and continues to set the stage for discoveries in G protein–coupled receptor signaling complexity. In this review, dedicated to the life and work of Athina Markou, we explore the role of $GABA_B$ receptors in depression, reward, and the convergence of these domains in anhedonia, a shared symptom of major depressive disorder and withdrawal from drugs of abuse. $GABA_B$ receptor expression and function are enhanced by antidepressants and reduced in animal models of depression. Generally, $GABA_B$ receptor antagonists are antidepressant-like and agonists are pro-depressive. Exceptions to this rule likely reflect the differential influence of $GABA_{B1}$ isoforms in depression-related behavior and neurobiology, including the anhedonic effects of social stress. A wealth of data implicate $GABA_B$ receptors in the rewarding effects of drugs of abuse. We focus on nicotine as an example. $GABA_B$ receptor activation attenuates, and deactivation enhances, nicotine reward and associated neurobiological changes. In nicotine withdrawal, however, $GABA_B$ receptor agonists, antagonists, and positive allosteric modulators enhance anhedonia, perhaps owing to differential effects of $GABA_{B1}$ isoforms on the dopaminergic system. Nicotine cue–induced reinstatement is more reliably attenuated by $GABA_B$ receptor activation. Separation of desirable and undesirable side effects of agonists is achievable with positive allosteric modulators, which are poised to enter clinical studies for drug abuse. $GABA_{B1}$ isoforms are key to understanding the neurobiology of anhedonia, whereas allosteric modulators may offer a mechanism for targeting specific brain regions and processes associated with reward and depression.

Key words: Anhedonia, Athina Markou, Depression, $GABA_B$ receptor, Nicotine, Reward

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The gamma-aminobutyric acid B ($GABA_B$) receptor was the first G protein–coupled receptor (GPCR) demonstrated as an obligate heterodimer: a landmark shift in the understanding of GPCR biology. Recent discoveries in $GABA_B$ receptor biology illustrate that much remains to be learned about this receptor, and it continues to pave the way for a greater understanding of GPCR signaling pathways and protein interactomes in general. GABA is the main inhibitory neurotransmitter in the brain, producing fast inhibitory neurotransmission through ionotropic $GABA_A$ receptors and slower inhibitory responses via metabotropic $GABA_B$ receptors (1,2). $GABA_B$ receptors are class C GPCRs, a group that includes metabotropic glutamate, calcium sensing, taste, and pheromone receptors. Functional $GABA_B$ receptors are formed from heterodimerization of the $GABA_{B1}$ and $GABA_{B2}$ subunits. They predominantly mediate their effects via $G\alpha_{i/o}$ proteins to inhibit adenylyl cyclase and $G\beta\gamma$ to gate ion channels, although evidence exists also for non-GPCR–mediated effects [see (2)]. They are widely distributed across the brain; are expressed as presynaptic, postsynaptic, and extrasynaptic heteroreceptors and interneuron autoreceptors; and have been demonstrated to have an equally wide range of neurophysiological functions [see (2,3)]. In the present article, we review the role of $GABA_B$ receptors in depression and reward, with a focus in the latter on nicotine dependence.

This article is dedicated to the life and work of Dr. Athina Markou. Dr. Markou's research and that of others, many of whom were Dr. Markou's collaborators or mentees, have affirmed an important role for $GABA_B$ receptors in depression, reward, and psychostimulant dependence. Indeed, Dr. Markou, together with George Koob, was among the first to work on the interface between these functions, identifying anhedonia as a common symptom of both psychostimulant withdrawal and depression (4,5). Her work promoted psychostimulant withdrawal anhedonia both as an animal model of depression (6) and as a critical factor contributing to nicotine dependence (7). Subsequently, Dr. Markou's work highlighted common neurobiological substrates, including $GABA_B$ receptors, that are altered in both depression and psychostimulant dependence [see (8) and Kenny *et al.* (9) in this issue]. In this article, we provide evidence to conclude that $GABA_B$ receptors are central to neurobiological processes underlying depression and reward and that new discoveries regarding the mechanisms of this complex receptor continue to promote $GABA_B$ receptors as a promising target for the development of therapeutics in these domains.

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$GABA_B$ RECEPTOR

The existence of the $GABA_B$ receptor was first proposed by the late Norman Bowery and colleagues in the early 1980s (10,11) based on findings of a GABA-mediated response insensitive to the $GABA_A$ receptor antagonist bicuculline but sensitive to baclofen. The receptor itself, however, was not cloned until 16 years later and even then only partially, with two isoforms (then thought to be splice variants) identified and named $GABA_BR1a$ and $GABA_BR1b$ (12). The amino acid sequence of the two isoforms differs only by the inclusion of two sushi domains at the N-terminus of the $GABA_{B1a}$ isoform, as both isoforms are transcribed from different promoter regions of the same gene, *Gabbr1* (13). In 1998, the $GABA_{B2}$ subunit was described concomitantly by a number of research groups [see (2)]. Coexpression of the two subunits rescued surface expression, agonist binding affinity, and effector coupling in recombinant systems, which were attenuated when the $GABA_{B1}$ subunit was expressed alone (12). This is because $GABA_{B1}$ subunits are retained in the endoplasmic reticulum in the absence of the $GABA_{B2}$ subunit (14), as the latter masks an endoplasmic reticulum retention motif in the $GABA_{B1}$ subunit (15,16). The $GABA_B$ receptor was thus the first described obligate GPCR heterodimer. Expression of the two $GABA_B$ subunits and their requisite heterodimerization is conserved across vertebrates and invertebrates, indicating the evolutionary importance of this mechanism, although variation in the pharmacological properties of $GABA_B$ receptor across species remains [see (17,18)].

Presynaptic effectors of $GABA_B$ receptors include voltage-gated calcium channels, whereby $GABA_B$ receptor activation inhibits the release of different neurotransmitters by reducing calcium influx. Presynaptic $GABA_B$ receptors also directly inhibit neurotransmitter release via interaction with components of exocytotic machinery, such as syntaxin-1 (19). Postsynaptic $GABA_B$ receptor effects are predominantly mediated by G protein–activated inwardly rectifying potassium (GIRK or Kir3) channels via regulators of G-protein signaling proteins, which mediate slow inhibitory postsynaptic currents (20–23) [see also (17)].

The molecular diversity of the $GABA_B$ receptor thus appears deceptively simple, predominantly composed per se of $GABA_{B1a,2}$ and $GABA_{B1b,2}$ receptor heterodimers [see (17)]. Complexity of the system, however, is augmented by the differential trafficking and neuroanatomical expression profile of $GABA_{B1}$ isoforms (24). The $GABA_{B1a,2}$ dimer is predominantly a presynaptic heteroreceptor and $GABA_{B1b,2}$ is a postsynaptic receptor, with both isoforms fulfilling autoreceptor functions in the hippocampus, amygdala, and thalamus (24–26). In layer 5 cortical neurons, this architecture is mostly preserved, although the predominant autoreceptor is $GABA_{B1a,2}$ (27). The sushi domains of the $GABA_{B1a}$ isoform are responsible for the axonal targeting of the $GABA_{B1a}$ isoform and coupling to presynaptic heteroreceptor effector systems (28,29).

Further complexity arises with the growing list of proteins that interact with $GABA_B$ receptors to form assemblies. The potassium channel tetramerization domain (KCTD) proteins KCTD8, KCDT12, KCDT12b, and KCDT16 selectively bind with $GABA_B$ receptors (30–33) and are now considered as core components of the $GABA_B$ receptor [see (34)]. KCTDs modulate $GABA_B$ receptor function by influencing desensitization, constitutive activity, and coupling of effector channels [reviewed in (17,34)]. $GABA_B$ receptors also form stable tetramers or higher order oligomeric assemblies (35), the functions of which are not yet clear (34). Recently, quantitative proteomics identified a further 20 previously undescribed proteins that interact with $GABA_B$ receptors (32). This work in particular defines $GABA_B$ receptors as complex macromolecular assemblies with core and peripheral interactors that influence effector system coupling, signaling duration, desensitization, surface expression, internalization, membrane anchoring, and localization or that have not yet had functions identified (32) [review in (34)]. Indeed, two new effector systems have recently been described: hyperpolarization-activated cyclic nucleotide-gated channels (32), and the capsaicin receptor transient receptor potential vanilloid type 1 (36). These complexes may, in the future, offer novel ways to pharmacologically target $GABA_B$ receptors and their specific effector systems. Pharmacological targeting of the $GABA_B$ receptor to date is achieved by agonists, antagonists, and allosteric modulators (see Supplement).

$GABA_B$ RECEPTORS IN DEPRESSION

There is robust evidence to indicate that $GABA_B$ receptors are involved in depression and/or the action of antidepressants; indeed, $GABA_B$ receptor antagonists have been proposed as an attractive target for the development of novel antidepressants for some time [see (3,37–42)]. Evidence for a role for $GABA_B$ receptors in depression includes the landmark work of eminent neuropharmacologists Andrzej Pilc, Richard Green, and Sam Enna, who showed with animal models that antidepressant treatments, including electroconvulsive shock therapy, enhanced the expression (43–49) and function (49,50) of $GABA_B$ receptors. Similarly, animal models of depression generally show reduced expression and/or function of $GABA_B$ receptors [e.g. (51,52), but see (53), reviewed in (38)]. In a recent example, unpredictable chronic mild stress reduced paraventricular nucleus $GABA_{B1}$ subunit expression and $GABA_B$ receptor–mediated postsynaptic currents as well as corticosterone release induced by injection of baclofen into the paraventricular nucleus, while the presynaptic inhibitory effects of baclofen on glutamatergic synapses were enhanced (54). In addition, chronically administered $GABA_B$ receptor antagonists, such as CGP36742 and SCH50911, upregulated $GABA_B$ receptor binding sites (55,56) to a similar degree to that of chronically administered desipramine (57).

Pharmacological and genetic deletion studies provide further support for a role of $GABA_B$ receptors in depression and antidepressant-like actions (Table 1). $GABA_B$ receptor antagonists have been widely shown to have antidepressant-like activity in animal models (Table 1), although baclofen was reported to display antidepressant-like effects in one study (58). Recent studies also propose that $GABA_B$ receptors may be implicated in the rapid antidepressant-like effects of *N*-methyl-D-aspartate receptor antagonists exemplified by ketamine (59–61), suggesting that the interaction between antidepressants and $GABA_B$ receptors may be somewhat independent of the antidepressant mechanism of action.

Genetic deletion of either the $GABA_{B1}$ or the $GABA_{B2}$ receptor subunits induces an antidepressant-like phenotype in the forced swim test (FST) in mice (62,63). The $GABA_B$