Published in final edited form as:
Adv Pharmacol. 2010 ; 58: 113–122. doi:10.1016/S1054-3589(10)58005-0.

Functional modulation of $GABA_B$ receptors by protein kinases and receptor trafficking

Miho Terunuma[1], **Menelas N. Pangalos**[2], and **Stephen J. Moss**[1,3]

[1] Department of Neuroscience, Tufts University School of Medicine, Boston, MA 02111

[2] Pfizer, Eastern Point Road, Groton, CT 06340

[3] Department of Neuroscience, Physiology and Pharmacology, University College London, Gower Street, London WC1E 6BT, UK

Abstract

$GABA_B$ receptors ($GABA_BR$) are heterodimeric G-protein coupled receptors (GPCRs) that mediate slow and prolonged inhibitory signals in the central nervous system. The signaling of GPCRs is under stringent control and is subject to regulation by multiple posttranslational mechanisms. The β-adrenergic receptor is a prototypic GPCR. Like most GPCRs prolonged exposure of this receptor to agonist induces phosphorylation of multiple intracellular residues that is largely dependent upon the activity of G protein-coupled receptor kinases (GRKs). Phosphorylation terminates receptor effector coupling and promotes both interaction with β-arrestins and removal from the plasma membrane via clathrin-dependent endocytosis. Emerging evidence for $GABA_BRs$ suggests that these GPCRs do not conform to this mode of regulation. Studies using both native and recombinant receptor preparations have demonstrated that $GABA_BRs$ do not undergo agonist-induced internalization and are not GRK substrates. Moreover whilst $GABA_BRs$ undergo clathrin-dependent constitutive endocytosis, it is generally accepted that their rates of internalization are not modified by prolonged agonist exposure. Biochemical studies have revealed that $GABA_BRs$ are phosphorylated on multiple residues within the cytoplasmic domains of both the R1 and R2 subunits by cAMP-dependent protein kinase and 5′AMP-dependent protein kinase (AMPK). Here we discuss the role that this phosphorylation plays in determining $GABA_BR$ effector coupling and their trafficking within the endocytic pathway and go on to evaluate the significance of $GABA_BR$ phosphorylation in controlling neuronal excitability under normal and pathological conditions.

Keywords

$GABA_B$ receptor; Kinase; Phosphorylation; Trafficking

1. Introduction

$GABA_BRs$ are GPCRs that mediate the slow and prolonged inhibitory action of GABA, the principal inhibitory neurotransmitter in the brain, via activation of Gαi- and Gαo-type heteromeric type G proteins. $GABA_BRs$ mediate their inhibitory action via multiple effectors; post-synaptically they activate inwardly rectifying K^+ channels (GIRKs), leading to

*Correspondence should be addressed to: Stephen J. Moss, Ph.D. Department of Neuroscience, Tufts University School of Medicine, MA 02111. stephen.moss@tufts.edu. Tel: +1-617-636-3976, Fax: +1-617-636-2413.

Conflict of Interest statement
The authors declare no conflict of interest.

hyperpolarization, whilst pre-synaptically they inhibit voltage-gated N/P/Q type Ca^{2+} channels, leading to reduced neurotransmitter release (Couve et al., 2000, 2004; Bettler et al., 2004, 2006). Through their activation of Gαi they also inhibit the activity of adenylate cyclase to reduce PKA signaling pathways.

Given the central roles of $GABA_BRs$ in mediating neuronal inhibition there is considerable interest in understanding the cellular mechanisms neurons use to modulate their activity. This is in determined in part by the efficacy of the effector coupling of $GABA_BRs$ and their residence time on the plasma membrane. Classically the signaling of monomeric GPCRs, as exemplified by the prototypic β-adrenergic receptor, is tightly controlled by agonist desensitization. Prolonged exposure to agonist leads to decreased effector coupling due to enhanced phosphorylation by G protein-coupled receptor kinases (GRKs). This decreased effector coupling ultimately leads to endocytosis followed by recycling or degradation (Ferguson, 2001; von Zastrow, 2003; Gainetdinov et al., 2003; Marchese et al., 2008). In this review we discuss the molecular mechanisms that neurons use to regulate the functional activity of $GABA_BRs$ and the roles that these processes play as determinants of the efficacy of neuronal inhibition.

2. Phosphorylation of $GABA_BR$ and its functional modulation

It is well documented that the activation and inactivation of GPCRs is modulated by the phosphorylation within the carboxyl (C)-terminus and the third intracellular loop by various protein kinases (Ferguson 2001; von Zastrow 2003; Marchese et al., 2008). In general, phosphorylation of GPCRs by intracellular kinases induces the desensitization of the receptor followed by interaction with cytosolic cofactor proteins called arrestins, which uncouple the receptor from G proteins. GPCRs are internalized from the plasma membrane principally via clathrin-dependent endocytosis. They are then recycled back to the plasma membrane for re-insertion or targeted for lysozomal degradation.

To evaluate the significance of this mode of regulation for $GABA_BRs$ measurements of phosphorylation have been performed in both expression systems and in neurons using labeling with ^{32}P-orthophosphate followed by immunoprecipitation with or without agonist exposure. Whilst $GABA_BRs$ exhibit significant levels of basal phosphorylation this is not subject to agonist-induced modulation. Consistent with this neither the R1 or R2 subunits are substrates of GRKs 1–4 when co-expressed in HEK-293 cells. The major intracellular domains of these proteins are not phosphorylated by purified GRKs *in vitro* (Perroy et al., 2003; Fairfax et al., 2004). In contrast to other GPCRs, $GABA_BRs$ are not GRK substrates and do not appear to undergo agonist-induced internalization. We discuss which kinases mediate $GABA_BR$ phosphorylation and consider the significance of this covalent modification in determining the efficacy of receptor signaling and trafficking itineraries. We then go on to assess the physiological significance of phosphorylation and its impact on $GABA_BR$ signaling under normal and pathological conditions.

I. PKA

The phosphorylation of GPCRs by PKA has been shown to regulate receptor activity (Bouvier et al., 1988; Moffet et al., 1996; Bunemann and Hosey 1999). For instance, for the β-adrenergic receptor and rhodopsin receptors, PKA phosphorylation enhances receptor desensitization by inducing internalization. Consistent with other GPCRs a role for PKA in mediating $GABA_BR$ receptor desensitization had been postulated prior to their structural characterization (Yoshimura et al., 1995). In agreement with this study a strong consensus site for PKA phosphorylation is found at serine 892 (S892) within the R2 subunit (Q-R-R-L-S-L). Studies using *in vitro* phosphorylation with purified PKA coupled with metabolic labeling of recombinant receptors expressed in fibroblast has confirmed that S892 is the sole site of

phosphorylation for cAMP-mediated phosphorylation within $GABA_BRs$. Using phospho-specific antibodies significant levels of basal phosphorylation of S892 are evident within the brain, a phenomenon that is dependent principally upon the activity of PKA (Couve et al., 2001).

The role of PKA-mediated phosphorylation in mediating $GABA_BR$ effector coupling has been examined by measuring their ability to activate GIRKs. Upon brief exposure to agonist phosphorylation of S892 via PKA decreases the time-dependent decrease (rundown) in the efficacy of $GABA_BR$- dependent activation of GIRKs in both HEK-293 cells and hippocampal neurons (Couve et al., 2001). This effect likely results from stabilization of $GABA_BRs$ on the neuronal plasma membrane. In contrast to the majority of GPCRs, PKA-mediated phosphorylation of S892 in the R2 subunit thus appears to promote $GABA_BR$ signaling. PKA regulation of $GABA_BR$ might not occur as a result of agonist stimulation but as a result of cAMP accumulation by neurotransmitters that activate Gαs-coupled receptors. It remains to be determined which signaling pathways mediate S892 phosphorylation and thus $GABA_BR$ effector coupling; however, it is well accepted that prolonged activation of $GABA_BRs$ via the activation of Gαi leads to decreased PKA activity. Consistent with this prolonged activation of $GABA_BRs$ leads to dephosphorylation of S892 and receptor degradation (Fairfax et al., 2004). Thus the phosphorylation status of S892, which is in part dependent upon agonist activation, is likely to play critical roles in maintaining $GABA_BR$ cell surface stability and the strength of synaptic inhibition.

II. PKC

PKC activity had long been known to attenuate $GABA_BR$ mediated inhibition of neurotransmitter release and receptor effector coupling (Dutar and Nicoll, 1988; Taniyama et al., 1991, 1992; Gahwiler et al., 1992). More recently the phosphorylation of R1 subunit by PKC has been reported by Bouvier and colleagues (Pontier et al., 2006). The activation of PKC induces the phosphorylation of R1 subunit followed by N-ethylmaleimide-sensitive fusion (NSF) protein dissociation from $GABA_BR$ and promotes desensitization. Like PKA, PKC phosphorylation does not induce $GABA_BR$ internalization. NSF is a molecular chaperone that is known to be crucial element in membrane fusion events. It has also been identified as a regulator of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) (Nishimune et al., 1998; Osten et al., 1998; Noel et al., 1999), the γ-aminobutyric acid (GABA) type A receptor ($GABA_AR$) (Goto et al., 2005) and β2 adrenergic receptor cell surface expression (Cong et al., 2001). In Chinese hamster ovary (CHO) cells $GABA_BR$ activity promotes PKC recruitment to the plasma membrane, inducing R1 subunit phosphorylation. Phosphorylation of R1 subunit is disrupted by preventing the binding of NSF to $GABA_BRs$ using selective peptides; the association of NSF to $GABA_BRs$ is clearly crucial for $GABA_BR$ phosphorylation. As measured in CHO cells recruitment of PKC dependent upon NSF blocked baclofen-induced G protein activation by $GABA_BRs$ but did not modify basal activity as measured using ^{35}S-GTP-γS binding. It remains to be determined which residues within $GABA_BRs$ are PKC substrates and to ascertain the relevance of this novel regulatory mechanism for neuronal $GABA_BRs$.

III. AMPK

It is evident that, in addition to PKA, $GABA_BRs$ are substrates for AMPK (Kuramoto et al, 2008). AMPK is a serine/threonine protein kinase that exists as a heterotrimer consisting of the catalytic α-subunit and regulatory β- and γ-subunits (Spasic et al., 2009). This kinase acts as an energy sensor that is rapidly activated when the cellular levels of AMP increase due to high metabolic activity or the pathological states of anoxia and ischemia (Kahn et al., 2005; Carling, 2005). To date the majority of AMPK substrates are metabolic enzymes; however, AMPK also binds with high affinity to the C-terminus of R1 but not R2 subunit. Interestingly,

AMPK phosphorylates the C-tails of both R1 and R2 subunits *in vitro*. Using mass spectrometry and Edman degradation analysis two phosphorylation sites in R1 subunit (S917/923), and one site in R2 subunit (S783) have been identified. The physiological relevance of this phosphorylation has been examined by measuring the effects of AMPK activity on the activation of GIRKs in both expression systems and neurons. This revealed that the phosphorylation of R2 subunit on S783 decreases the desensitization of $GABA_BRs$ by stabilizing the receptor complex at the plasma membrane. These results suggest that, similar to PKA, the AMPK-mediated phosphorylation of $GABA_BRs$ either inhibits receptor endocytosis or increases receptor exocytosis to maintain synaptic inhibition.

3. Phosphorylation-independent desensitization of $GABA_BRs$ by protein kinases

Desensitization to prevent overstimulation is a common feature of GPCRs. For most GPCRs, a time-dependent desensitization of the receptor appears to be mediated by direct phosphorylation of the GPCRs by GRK followed by arrestin and dynamin-dependent receptor internalization via clathrin-coated vesicle and recycling/degradation signaling pathways (von Zastrow, 2003; Marchise et al., 2006). Whilst $GABA_BRs$ do not appear to be directly phosphorylated by GRKs, GRK4 and GRK5 have been reported to play a central role in agonist-induced desensitization (Perroy et al., 2003; Kanaide et al., 2007). For instance, the suppression of GRK4 expression in cerebellar granule cells strongly inhibits $GABA_BR$ desensitization (Perroy et al 2003). Similarly, in *Xenopus oocytes* and baby hamster kidney (BHK) cells, expression of $GABA_BR$ and GIRKs does not result in desensitization unless co-expressed with GRK4 or GRK5 (Kanaide et al., 2007). Interestingly, the association of GRKs to R2 subunits is also observed but the $GABA_BR$ phosphorylation is independent of GRK association (Perroy et al., 2003; Fairfax et al., 2004; Kanaide et al., 2007). Unlike most GPCRs, GRKs may thus function as anchoring proteins to regulate $GABA_BR$ activity but not phosphorylation.

4. $GABA_BR$ endocytic sorting and the control of receptor cell surface stability

It is generally agreed that $GABA_BRs$ do not show agonist-induced endocytosis; however, they do exhibit significant rates of constitutive endocytosis (Couve et al., 2001; Perroy et al., 2003; Fairfax et al., 2004; Vargas et al., 2008). Under basal conditions $GABA_BRs$ endocytose as dimers via clathrin- and dynamin-dependent mechanisms and localize to Rab11-positive recycling endosomes. After constitutive endocytosis, large numbers of $GABA_BRs$ recycle back to the plasma membrane to maintain steady-state cell surface numbers, presumably reflecting the long cell surface half-lives for these proteins as measured via biotinylation (Fairfax et al., 2004; Vargas et al., 2008). Interestingly endocytosis is detected only in dendrites, not in axons. The mechanisms underlying this compartmentalization of $GABA_BR$ endocytosis remain obscure; however, R1 subunit has many splice variants, which likely results in multiple distinct modes of phosphorylation. Consistent with steady-state measurement $GABA_BR$ endocytosis is agonist-independent; however, cell surface accumulation is dramatically reduced by exposure to glutamate via a mechanism dependent upon the activity of the proteasome (Vargas et al., 2008). In this study glutamate treatment did not result in enhanced intracellular accumulation of $GABA_BRs$, suggesting that this excitatory neurotransmitter may regulate lysozomal targeting of $GABA_BRs$. Further studies are needed to determine how glutamate treatment of neurons leads to degradation of $GABA_BRs$.

5. $GABA_BR$ phosphorylation and diseases

I. Addiction

Recently $GABA_BR$ agonist and allosteric modulators have been successfully used to treat the symptoms associated with withdrawal from cocaine, opiates, nicotine and ethanol (Filip and

Frankowska, 2008; Frankowska et al, 2009; Addolorato et al, 2009). This may be due to the phosphorylation of $GABA_BRs$. Kalivas and colleagues reported that repeated cocaine administration leads to an increase in basal extracellular GABA in the nucleus accumbens and to dephosphorylation of R2 subunits (Xi et al., 2003). Because prolonged activation of $GABA_BRs$ decreases cAMP production and PKA activation through Giα, elevated extracellular GABA by repeated cocaine injection may regulate S892 phosphorylation in R2 subunit. In this study, the authors performed an immunoprecipitation assay followed by immunoblotting using anti-phospho-serine antibody. Additional experiments using phospho-specific antibody against S892 and S783 is clearly essential. Repeated cocaine administration can regulate the release of various neurotransmitters, and thus would also be able to regulate many of the second messenger kinases that phosphorylate $GABA_BRs$.

II. Ischemia

Our group recently demonstrated that the phosphorylation of $GABA_BRs$ by AMPK indicates a possible neuroprotective role for $GABA_BRs$ (Kuramoto et al., 2007). AMPK is expressed in neurons throughout the brain. Rapid AMPK activation has been observed following ischemia, hypoxia, and glucose deprivation (Culmsee et al., 2001; Gadalla et al., 2004; Kahn et al., 2005; Carling, 2005; Li et al., 2007; Spasic et al., 2009). Phosphorylation of S783 but not S892 in R2 subunit has been documented in the CA3 and dentate gyrus of hippocampus after ischemic injury induced by MCAO (middle cerebral artery occlusion). The overexpression of R2 subunits in cultured hippocampal neurons also shows phosphorylation of S783 and enhanced neuronal survival in experiments using a model of anoxia (oxygen-glucose deprivation). Since mutation of S783 to alanine significantly decreases neuronal survival compared to wild-type in this model, phosphorylation of S783 in R2 subunit is likely to be a critical mechanism for neuronal survival.

6. Conclusion

$GABA_BRs$ are unique GPCRs that function as heterodimers composed of R1 and R2 subunits. They mediate slow and prolonged inhibitory signals. Deficits in $GABA_BR$ function have been reported in many neurological and psychiatric disorders. We have discussed here current findings on the involvement of protein kinases in $GABA_BR$ modulation; however, the existence of phosphorylation-dependent $GABA_BR$ endocytosis is still unclear. Identifying the molecular machinery that regulates $GABA_BR$ trafficking is thus key in developing novel therapeutics to treat neurological and psychiatric disorders.

Acknowledgments

MT is recipient of a National Scientist Development award from the American Heart Association. SJM supported by National Institute of Neurological Disorders and Stroke Grants NS047478, NS048045, NS051195, NS056359, NS065725 and NS054900.

Abbreviations

AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPK	AMP-activated protein kinase
BHK	baby hamster kidney
cAMP	cyclic adenosine monophosphate
CHO	Chinese hamster ovary
GABA	γ-aminobutyric acid

$GABA_BR$	$GABA_B$ receptor
GIRKs	G protein-activated inwardly rectifying K^+ channels
GPCRs	G protein-coupled receptors
GRKs	G protein-coupled receptor kinases
HEK	human embryonic kidney
MCAO	middle cerebral artery occlusion
NSF	N-ethylmaleimide-sensitive fusion
PKA	cAMP-dependent protein kinase
PKC	protein kinase C

References

Addolorato G, Leggio L, Cardone S, et al. Role of the $GABA_B$ receptor system in alcoholism and stress; focus on clinical studies and treatment perspectives. Alcohol 2009;43:559–563. [PubMed: 19913201]

Bettler B, Kaupmann K, Mosbacher J, et al. Molecular structure and physiological functions of $GABA_B$ receptors. Physiol Rev 2004;84:835–867. [PubMed: 15269338]

Bettler B, Tiao JY. Molecular diversity, trafficking and subcellular localization of $GABA_B$ receptors. Pharmacol Ther 2006;110:533–543. [PubMed: 16644017]

Bouvier M, Hausdorff WP, De Blasi A, et al. Removal of phosphorylation sites from the β2-adrenergic receptor delays the onset of agonist-promoted desensitization. Nature 1988;333:370–373. [PubMed: 2836733]

Bunemann M, Hosey MM. G-protein coupled receptor kinases as modulators of G-protein signaling. J Physiol 1999;517:5–23. [PubMed: 10226145]

Carling D. AMP-activated protein kinase; balancing the scales. Biochimie 2005;87:87–91. [PubMed: 15733742]

Cong M, Perry SJ, Hu LA, et al. Binding of the beta2 adrenergic receptor to N-ethylmaleimide-sensitive factor regulates receptor recycling. J Bio Chem 2001;276:45145–45152. [PubMed: 11577089]

Couve A, Moss SJ, Pangalos MN. GABAB rceptors: a new aparadigm in G protein signaling. Mol Cell Neurosci 2000;16:296–312. [PubMed: 11085869]

Couve A, Thomas P, Calver AR, et al. Cyclic AMP-dependent protein kinase phosphorylation facilitates $GABA_B$ receptor-effector coupling. Nat Neurosci 2001;5:415–424. [PubMed: 11976702]

Couve A, Calver AR, Fairfax BP, et al. Unravelling the unusual signaling properties of the $GABA_B$ receptor. Biochem Pharm 2004;68:1527–1536. [PubMed: 15451395]

Culmsee C, Monnig J, Kemp BE, et al. AMP-activated protein kinase is highly expressed in neurons in the developing rat brain and promotes neuronal survival following glucose deprivation. J Mol Neurosci 2001;17:45–58. [PubMed: 11665862]

Dutar P, Nicoll RA. Pre- and postsynaptic GABAB receptors in the hippocampus have different pharmacological properties. Neuron 1988;1:585–591. [PubMed: 2856099]

Fairfax BP, Pitcher JA, Scott MG, et al. Phosphorylation and chronic agonist treatment atypically modulate $GABA_B$ receptor cell surface stability. J Biol Chem 2004;279:12565–12573. [PubMed: 14707142]

Ferguson SSG. Evolving concepts in G protein-coupled receptor endocytosis: The role in receptor desensitization and signaling. Pharmacol Rev 2001;53:1–24. [PubMed: 11171937]

Filip M, Frankowska M. $GABA_B$ receptors in drug addiction. Pharmacol Rep 2008;60:755–770. [PubMed: 19211967]

Frankowska M, Nowak E, Fillip M. Effects of $GABA_B$ receptor agonists on cocaine hyperlocomotor and sensitizing effects in rats. Pharmacol Rep 2009;61:1042–1049. [PubMed: 20081239]

Gadalla AE, Pearson T, Currie AJ, et al. AICA ribose both activates AMP-activated protein kinase and competes with adenosine for the nucleotide transporter in the CA1 region of the rat hippocampus. J Neurochem 2004;88:1272–1282. [PubMed: 15009683]

Gainetdinov RR, Bohn LM, Sotnikova TD, et al. Dopaminergic supersensitivity in G protein-coupled receptor kinase 6-deficient mice. Neuron 2003;24:291–303. [PubMed: 12718862]

Goto H, Terunuma M, Kanematsu T, et al. Direct interaction of N-ethylmaleimide-sensitive factor with GABA(A) receptor beta subunits. Mol Cell Neurosci 2005;30:197–206. [PubMed: 16095914]

Kahn BB, Alquier T, Carling D, et al. AMP-activated protein kinase; ancient energy gauge provides clues to modern understanding of metabolism. Cell Metab 2005;1:15–25. [PubMed: 16054041]

Kanaide M, Uezono Y, Matsumoto M, et al. Desensitization of $GABA_B$ receptor signaling by formation of protein complexes of $GABA_{B2}$ subunit with GRK4 or GRK5. J Cell Physiol 2007;210:237–245. [PubMed: 17013811]

Kuramoto N, Wilkins ME, Fairfax BP, et al. Phospho-dependent functional modulation of $GABA_B$ receptors by the metabolic sensor AMP-dependent protein kinase. Neuron 2007;53:233–247. [PubMed: 17224405]

Li J, Zeng Z, Viollet B, et al. Neuroprotective effects of adenosine monophosphate-activated protein kinase inhibition and gene deletion in stroke. Stroke 2007;38:2992–2999. [PubMed: 17901380]

Marchese A, Paing MM, Temple BR, et al. G protein-coupled receptor sorting to endosomes and lysosomes. Annu Rev Pharmacol Toxicol 2008;48:601–629. [PubMed: 17995450]

Moffett S, Adam L, Bonin H, et al. Palmitoylated cysteine 341 modulates phosphorylation of the β2-adrenergic receptor by the cAMP-dependent protein kinase. J Biol Chem 1996;271:21490–21497. [PubMed: 8702933]

Nishimune A, Isaac JT, Molnar E, et al. NSF binding to GluR2 regulates synaptic transmission. Neuron 1998;21:87–97. [PubMed: 9697854]

Noel J, Ralph GS, Pickard L, et al. Surface expression of AMPA receptors in hippocampal neurons is regulated by an NSF-dependent mechanism. Neuron 1999;23:365–376. [PubMed: 10399941]

Osten P, Srivastava S, Inman GJ, et al. The AMPA receptor GluR2 C terminus can mediate a reversible, ATP-dependent interaction with NSF and alpha- and beta-SNAPs. Neuron 1998;21:99–110. [PubMed: 9697855]

Perroy J, Adam L, Qanbar R, et al. Phosphorylation-independent desensitization of $GABA_B$ receptor by GRK4. EMBO J 2003;22:3816–3824. [PubMed: 12881416]

Pontier SM, Lahaie N, Ginham R, et al. Coordinated action of NSF and PKC regulates $GABA_B$ receptor signaling efficacy. EMBO J 2006;25:2698–2709. [PubMed: 16724110]

Spasic MR, Callaerts P, Norga KK. AMP-activated protein kinase (AMPK) molecular crossroad for metabolic control and survival of neurons. Neuroscientist 2009;15:309–316. [PubMed: 19359670]

Taniyama K, Takeda K, Ando H, et al. Expression of the GABAB receptor in Xenopus oocytes and desensitization by activation of protein kinase C. Adv Exp Med Biol 1991;287:413–420. [PubMed: 1662013]

Taniyama K, Niwa M, Kataoka Y, et al. Activation of protein kinase C suppresses the gamma-aminobutyric acid b receptor-mediated inhibition of the vesicular release of noradrenaline and acetylcholine. J Neurochem 1992;58:1239–1245. [PubMed: 1312571]

Vargas KJ, Terunuma M, Tello JA, et al. The availability of surface $GABA_B$ receptors is independent of γ-aminobutyric acid but controlled by glutamate in central neurons. J Biol Chem 2008;283:24641–24648. [PubMed: 18579521]

Von Zastrow M. Mechanisms regulationg membrane trafficking of G protein-coupled receptors in the endocytic pathway. Life Sciences 2003;74:217–224. [PubMed: 14607249]

Xi ZX, Ramamoorthy S, Shen H, et al. GABA transmission in the nucleus accumbens is altered after withdrawal from repeated cocaine. J Neurosci 2003;23(8):3498–3505. [PubMed: 12716959]

Yoshimura M, Yoshida S, Taniyama K. Desensitization by cyclic AMP-dependent protein kinase of $GABA_B$ receptor expressed in Xenopus Oocytes. Life Sciences 1995;57:2397–2401. [PubMed: 8847960]