Chapter 8
$GABA_B$ Receptor Functions in the Mesolimbic Dopamine System

Arnaud L. Lalive and Christian Lüscher

Abstract $GABA_B$ receptors are expressed in neurons of the dopamine system where they bidirectionally modulate activity and release of glutamate, GABA, and dopamine itself. Dopamine has many functions including signaling of salient external stimuli and prediction errors that optimize decision-making, as well as motivation and initiation of movement. $GABA_B$ receptors thus exert a second-order modulation, with effects on locomotion, motivation, and reward learning. Moreover, recent findings indicate that neuronal activity may induce a plasticity of $GABA_B$ receptor signaling. In this chapter, we review the structural and functional features of $GABA_B$ receptor signaling in the dopaminergic system, from subcellular specialization to plasticity and fine-tuning of mesolimbic circuits. Beyond a physiological role $GABA_B$ receptors may also affect disease, such as addiction. $GABA_B$ receptors may therefore constitute an interesting target for pharmacological interventions to treat this condition.

Keywords $GABA_B$ receptor • Synaptic plasticity • Dopamine • Ventral tegmental area • Addiction • Mesolimbic system

A.L. Lalive (✉)
The Gladstone Institutes, San Francisco, CA 94158, USA
e-mail: arnaud.lalive@gmail.com

C. Lüscher (✉)
Department of Basic Neurosciences, Medical Faculty,
University of Geneva, Geneva 1211, Switzerland

Department of Clinical Neurosciences, Clinic of Neurology,
Geneva University Hospital, Geneva 1211, Switzerland
e-mail: christian.luscher@unige.ch

© Springer International Publishing Switzerland 2016

G. Colombo (ed.), *$GABA_B$ Receptor*, The Receptors 29,
DOI 10.1007/978-3-319-46044-4_8

8.1 The Midbrain DA System

8.1.1 Projection- and Input-Specific DA Populations

The midbrain dopamine (DA) system has its origin in two major nuclei: the Ventral Tegmental Area (VTA) and the Substantia Nigra compacta (SNc), which are anatomically and functionally distinct. The VTA DA neurons, close to the midline at the caudal end of the midbrain, project most notably to the Nucleus Accumbens (NAc) and Prefrontal Cortex (PFC), forming the mesocorticolimbic system. Increased DA activity is typically associated with positive outcome, whereas DA inhibition is aversive (Schultz 1998; Tan et al. 2012; van Zessen et al. 2012). DA neurons of the SNc are located lateral to the VTA, project to the dorsal striatum (the mesostriatal system) where they modulate locomotion. DA neurons also receive reciprocal inputs from their striatal target; the dorsal striatum mostly projects to the SNc, the NAc preferentially targets the VTA. Additionally, nuclei associated with motivational states like the dorsal raphe and the lateral hypothalamus selectively target the VTA over the SNc, further differentiating these two populations. In comparison, both DA nuclei receive equal projections from the cortex (Watabe-Uchida et al. 2012).

8.1.2 VTA Microcircuit

The VTA contains three cell types: DA, γ-aminobutyric acid (GABA)-ergic, and glutamatergic. The DA neurons form 80 % of the total population. The GABAergic neurons are fewer and provide a major inhibitory input to DA neurons (Johnson and North 1992a). The functional relevance of this microcircuit was initially demonstrated by showing that μ-opioid receptors specifically inhibit GABA neurons, leading to the disinhibition of DA neurons. Lastly, a small population of glutamatergic neurons forms local synapses with DA and GABA neurons (Dobi et al. 2010).

The recent development of transgenic mouse lines and optogenetics has allowed investigators to manipulate neuronal populations of the VTA in vivo and measure their impact on behavior, further validating the functional organization of the VTA microcircuit. For example, direct activation of DA neurons is sufficient to drive reward-related behaviors (Tsai et al. 2009; Adamantidis et al. 2011). In contrast, activation of GABA neurons inhibits DA firing and is sufficient to drive aversive behavioral responses (Tan et al. 2012; van Zessen et al. 2012). Finally, activation of the local glutamatergic population excites DA neurons and is rewarding (Wang et al. 2015).

8.1.3 Inputs to VTA Neurons

In the VTA, both DA and GABAergic populations receive quantitatively similar proportions of excitatory and inhibitory inputs from outside the VTA (Beier et al. 2015). Major excitatory inputs include the frontal cortex, central amygdala,

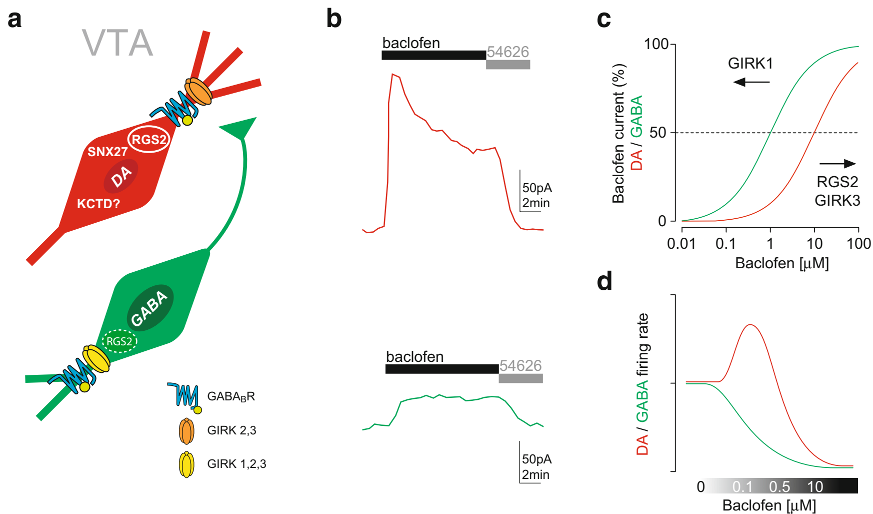

Fig. 8.1 Cell-type-specific GABA$_B$ receptor signaling in the VTA. (**a**) VTA microcircuit depicting GABA neuron (*green*) inhibition onto DA neuron (*red*), and cell-type-specific expression of proteins involved in GABA$_B$ receptor signaling. (**b**) Example voltage clamp recordings of maximal baclofen-evoked currents (300 µM) in DA (*red*, *upper panel*) and GABA (*green*, *lower panel*) neurons. Currents are blocked by GABA$_B$ receptor antagonist CGP54626 (2 µM). (**c**) Dose–response curve for baclofen in DA (*red*) and GABA (*green*) neurons, showing the difference in EC50. Insets indicate relevant proteins and their effect on coupling efficiency. (**d**) Schematic representation of DA (*red*) and GABA (*green*) neuron firing rate to increasing concentrations of baclofen [Traces in (**b**) reproduced from Labouèbe et al. 2007]

hippocampal septum, lateral habenula, and dorsal raphe, while major inhibitory inputs comprise the Nac, ventral pallidum, and globus pallidus. However, specific inputs from a given region may be qualitatively biased toward one cell type. For example, the GABAergic projection from the NAc preferentially inhibits VTA GABA neurons, and eventually disinhibits DA neurons (Xia et al. 2011; Bocklisch et al. 2013). Therefore, the ultimate DA output is controlled by balanced modulation of both DA and GABA neurons (Fig. 8.1).

8.1.4 GABA$_B$ Receptors in the Midbrain DA System

GABA$_B$ receptors are enriched across DA neurons of the midbrain, and also found in VTA GABA neurons, whereas their presence in VTA glutamatergic neurons remains to be established. It has been proposed that local and long-range inhibitory inputs to DA neurons have a specialization with synapses that contain only GABA$_A$ or GABA$_B$ receptors, respectively (Sugita et al. 1992; Johnson and North 1992b; Cameron and Williams 1993). However, recent investigations have suggested the presence of GABA$_A$ receptors at all inhibitory synapses in DA neurons. For example, optogenetic activation of long-range projections from the NAc evokes GABA$_A$ receptor-mediated inhibitory postsynaptic currents (IPSCs) in VTA DA neurons (Bocklisch et al. 2013).

Additionally, in vivo electrical stimulation of inhibitory nuclei targeting the SNc evokes a combined $GABA_A$, $GABA_B$ receptor-mediated inhibitory postsynaptic potential (IPSP) (Brazhnik et al. 2008). Whether VTA GABA neurons can activate $GABA_B$ receptors in DA neurons remains to be investigated. Dendritic $GABA_B$ receptors are typically extrasynaptically located (Boyes and Bolam 2003; Koyrakh et al. 2005), therefore a single pulse of stimulation evokes mostly $GABA_A$ receptor-mediated currents in the VTA. Higher intensity and frequency stimulation is usually required to drive GABA spillover outside the synaptic cleft and reach extrasynaptic $GABA_B$ receptors, suggesting that only sustained GABA release engages $GABA_B$ receptor signaling, independently of the synaptic input.

8.2 $GABA_B$ Receptor Signaling in the Midbrain

8.2.1 Common Features of $GABA_B$ Receptor Signaling

8.2.1.1 $GABA_B$ Receptor Structure and Main Effectors

Functional $GABA_B$ receptors are heterodimers that require the assembly of one $GABA_{B1}$ isoform (1a or 1b) with $GABA_{B2}$ (Jones et al. 1998; White et al. 1998; Kaupmann et al. 1998; see also Chap. 4 of this book). The $GABA_{B1a}$ subunit differs from $GABA_{B1b}$ by the expression of two sushi domains, which guide trafficking to axon terminals. Accordingly, $GABA_{B1a/2}$ receptors are mainly found presynaptically, whereas postsynaptic compartments mostly express $GABA_{B1b/2}$ dimers (Vigot et al. 2006). Because $GABA_B$ receptor subunit composition is similar across most neurons, any variability in $GABA_B$ receptor signaling is likely to be accounted for by associated proteins.

Both $GABA_{B1a/2}$ and $GABA_{B1b/2}$ similarly couple to $G_{i/o}$ protein. Gα inhibits the adenylate cyclase pathway while Gβγ gates ion channels. In presynaptic boutons, $GABA_B$ receptors decrease neurotransmitter release via Gβγ-mediated closing of Voltage-Gated Ca^{2+} (CaV) channels and direct interaction with the release machinery. Postsynaptically, the major effect of Gβγ is the opening of G protein-activated inwardly rectifying K^+ channels (GIRK, also known as Kir3), which hyperpolarize the membrane and decrease neuronal excitability (Bettler et al. 2004; Lüscher et al. 1997). (For a more detailed description of $GABA_B$ receptor signaling, see Chap. 6 of this book).

8.2.1.2 Macromolecular Signaling Complex and Associated Proteins

Accumulating evidence suggests that $GABA_B$ receptors and associated proteins form macromolecular complexes to promote the specificity of spatial and temporal control of signaling (Doupnik et al. 2004). Electron microscopy, co-immunoprecipitation, as well as bioluminescence and fluorescence resonance energy transfer experiments initially revealed close interactions between $GABA_B$ and GIRK subunits, suggesting the existence of those complexes (David et al. 2006; Fowler et al. 2007; Ciruela et al. 2010).

These approaches also identified the interaction of GABA$_B$ receptors and GIRK channels with Regulator of G protein signaling (RGS) proteins (Fowler et al. 2007). RGS provide powerful modulation of the coupling efficiency between GPCR and effectors by accelerating the activation and deactivation kinetics of G proteins, and have also been proposed to influence signaling desensitization, a process of signal attenuation upon receptor activation (Mutneja et al. 2005). For most G protein-coupled receptors (GPCR), desensitization is expressed by rapid agonist-induced internalization of the receptor. However GABA$_B$ receptors behave differently, and desensitization mechanisms remain elusive (Couve et al. 2002). More recently, affinity purification assays combined with quantitative mass spectrometry from native membrane preparations allowed the identification of four KCTD (K^+ Channel Tetramerization Domain-containing) proteins as auxiliary subunits of the GABA$_B$ receptors (Schwenk et al. 2010). KCTDs bind to the GABA$_{B2}$ subunit and modulate coupling, onset kinetics and desensitization of receptor signaling (Turecek et al. 2014). Further functional proteomics analyses revealed co-assembly with unsuspected partners like HCN (hyperpolarization-activated cyclic nucleotide-gated) channels. Surprisingly, no physical interaction was found between GABA$_B$ receptors or KCTD proteins and GIRK channels despite being major effector of GABA$_B$ receptors (Schwenk et al. 2016).

Altogether, there are many proteins that actively shape GABA$_B$ receptor signaling and even more possible combinations to build macromolecular complexes. Such abundance allows region and cell-type-specific variability of GABA$_B$ receptor functional expression, which is highly relevant in the midbrain DA system.

8.2.2 Cell-Type-Specific GABA$_B$ Receptor Signaling in the Midbrain

8.2.2.1 Differences in GABA$_B$ Receptor Signaling in VTA DA and GABA Neurons

In the VTA both DA and GABA neurons express GABA$_B$ receptors, however there are a number of functional differences that can be assessed by recording from VTA neurons in acute brain slices and applying baclofen, a GABA$_B$ receptor agonist, to evoke GIRK currents. First, DA neurons have a much lower sensitivity to baclofen, measured by an EC50 value (the concentration required to reach 50 % of the maximal response) ten-fold higher than in GABA neurons. Yet, the peak current evoked by a saturating concentration of baclofen is around three-fold larger in DA neurons. Lastly, in DA neurons, baclofen-evoked currents desensitize by around 40 % over minutes, whereas GABA neurons show a steady current upon continuous baclofen application (Cruz et al. 2004). These three differences in GABA$_B$ receptor signaling have been partially explained by differential composition and expression levels of proteins involved in GABA$_B$ receptor macromolecular signaling complex, which we review here (Table 8.1). They also provide the mesocorticolimbic system with a bidirectional handle on DA output, which will be discussed later.

Table 8.1 Cell-type-specific expression of proteins modulating $GABA_B$ receptor signaling in the midbrain DA system

	DA	GABA	References
GIRK	2a (SNc only)	1	Inanobe et al. (1999)
	2c	2c	Cruz et al. (2004)
	3	3	Labouèbe et al. (2007)
RGS	2		Labouèbe et al. (2007)
	4	4	
KCTD	12?	12?	Metz et al. (2011)
	16?	16?	
SNX	27	27?	Munoz and Slesinger (2014)
HCN	high	low	Lacey et al. (1989)

8.2.2.2 Cell-Type-Specific GIRK Channel Expression

VTA DA and GABA neurons express a specific set of GIRK channel subunits. Of the four known GIRK subunits, GIRK1, 2, and 3 are found in the brain, whereas GIRK4 expression is low and probably functionally irrelevant (Wickman et al. 2000). GIRK channels assemble as heterotetramers formed by two pairs of two subunits (1/2, 1/3, 2/3), or GIRK2 homotetramers, with GIRK2 available in three isorforms, GIRKa-c (Lüscher and Slesinger 2010). GIRK2-containing channels seem to be most commonly expressed throughout the brain, as knocking-out GIRK2 ablates almost entirely GIRK-mediated currents in many different cell types, including midbrain DA and GABA neurons (Lüscher et al. 1997; Arora et al. 2010; Cruz et al. 2004; Hearing et al. 2013).

VTA GABA neurons express GIRK1, 2c, and 3 subunits, whereas VTA and SNc DA neurons do not express GIRK1, as observed by single cell RT-PCR and electron microscopy (Inanobe et al. 1999; Cruz et al. 2004; Labouèbe et al. 2007). The presence of GIRK1 partially explains why $GABA_B$ receptors have a higher coupling efficiency in GABA neurons. Indeed, ectopic expression of GIRK1 in VTA DA neurons reduces the EC50 value for baclofen-evoked GIRK currents. Conversely, the same result is obtained by knocking out GIRK3 from DA neurons, suggesting that GIRK1 increases, whereas GIRK3 decreases the coupling efficiency of $GABA_B$ receptors (Labouèbe et al. 2007).

Cell-type-specific GIRK channel composition is also found among the midbrain DA population. VTA DA neurons express mostly GIRK2c/3 heteromers, whereas SNc DA neurons express both GIRK2a and 2c isoforms and form GIRK2a/2c homomers (Inanobe et al. 1999). Although not directly compared, maximal currents and desensitization rate seem similar overall in both populations (VTA: Labouèbe et al. 2007; SNc: Arora et al. 2010). Accordingly, GIRK3 knockout does not affect amplitude or desensitization in SNc DA neurons, although the latter was not systematically quantified (Arora et al. 2010). Thus, it appears that GIRK channel composition broadly influences coupling efficiency, whereas a potential role for GIRK1 in desensitization remains to be explored.

8.2.2.3 Cell-Type-Specific RGS Expression

Another major difference observed so far is the selective expression of RGS2 in VTA DA neurons versus GABA neurons. Whereas RGS4 is present in both, RGS2 associates with the GIRK3 subunit and acts as a brake on coupling efficiency of GABA$_B$ receptor signaling in DA neurons. Either inhibiting RGS proteins or knocking out RGS2 results in lower EC50 values for baclofen-evoked GIRK currents in DA neurons, similar to GIRK3 knockout. RGS2 and GIRK3 double knockout do not further decrease the EC50 value, suggesting that RGS2 decreases the coupling efficiency through its interaction with GIRK3 (Labouèbe et al. 2007).

8.2.2.4 KCTD

Notably, neither GIRK3 knockout, RGS2 knockout nor their combination in DA neurons fully recapitulates the high coupling efficiency observed in GABA neurons. Therefore, other components of the signaling complex must account for this cell-type-specific aspect GABA$_B$ receptor signaling. The missing piece of the puzzle could very well be found in a newly identified function of KCTD proteins, as auxiliary subunits for GABA$_B$ receptors (Schwenk et al. 2010). Affinity purification assays have identified four members of the KCTD family that interact with GABA$_{B2}$: KCTD8, 12, 12b, and 16. In cultured hippocampal neurons, all four KCTD sharpen the rise-time of GIRK currents. KCTD12 and 12b also shorten current onset, and most interestingly, strongly increase the desensitization rate. The acceleration of signal transduction is mediated by the binding of KCTDs to G proteins, keeping them close to and stabilizing GABA$_B$ receptors. The pronounced desensitization is due to the ability of KCTD12 and 12b, but not 8 or 16, to bind activated Gβγ proteins and uncouple them from GIRK channels (Turecek et al. 2014). KCTD12 and 16 are enriched in the VTA (Metz et al. 2011), however cell-type-specific expression patterns remain so far unexplored in this same region. Selective expression of KCTD12 in DA neurons is a likely molecular candidate to explain the signature desensitizing GIRK currents in these cells, and differential KCTD expression may also explain discrepancies in coupling efficiency in GABA versus DA neurons.

8.2.2.5 Sorting Nexin 27

The expression of GIRK2c/3 heteromers in VTA DA neurons allows their targeting by Sorting Nexin 27 (SNX27), an endosomal protein involved in the trafficking of several G protein-coupled receptors (GPCR) (Joubert et al. 2004; Lauffer et al. 2010). SNX27 contains a PDZ domain that selectively associates with the C-terminal PDZ-binding motif on GIRK2c and GIRK3 subunits (Balana et al. 2013; Lunn et al. 2007). In mice lacking SNX27 only in DA neurons, maximal baclofen currents are

blunted, presumably due to a decreased surface expression of GIRK channels (Munoz and Slesinger 2014). SNX27 is also expressed in non-DA neurons of the VTA, and might therefore fulfill a similar function in GABA neurons.

8.2.2.6 HCN Channels

Midbrain DA neurons, but not GABA neurons express HCN channels, which enable the pacemaker-like tonic firing of SNc DA neurons (Neuhoff et al. 2002; Khaliq and Bean 2010). HCN channels co-assemble with $GABA_{B2}$ via KCTD16. It has been suggested that $GABA_B$ receptor activation leads to HCN channel opening over several hundreds of milliseconds, closely following the timescale of G protein signaling. HCN opening potentially decrease the amplitude and accelerates the decay of GIRK-mediated postsynaptic potentials (Schwenk et al. 2016). The mechanistic underpinnings of this phenomenon remain to be explored. For example, HCN channels are typically activated by hyperpolarization, which is driven by GIRK channels. Therefore it is possible that HCN channel opening is unrelated to $GABA_B$ receptor signaling and simply responds to GIRK activation, providing a depolarizing drive. However HCN channels are also gated by cyclic Adenosine Monophosphate (cAMP), which is decreased by Gαi/o-mediated inhibition of adenylate cyclase, so in theory $GABA_B$ receptor activation could shift the threshold for HCN opening toward more hyperpolarized potentials. Another possibility is that $GABA_B$ receptor signaling directly interacts with HCN channels, as with main effectors like GIRK and CaV channels. This distinction is crucial to understanding the functional relevance of the interplay between $GABA_B$ receptors and HCN channels. Regardless of mechanism, this DA-specific effect may also shape the unique $GABA_B$ receptor-GIRK signaling characteristics observed in these cells.

8.3 $GABA_B$ Receptor Modulation of DA Neuron Activity

8.3.1 DA Neuron Firing Patterns

DA neurons typically display two firing patterns: tonic firing, a regular pacemaker-like rhythm (1–8 Hz), and burst or phasic firing, characterized by several action potentials at higher frequencies (>15 Hz), also known as phasic firing (Grace and Bunney 1984a, b). Tonic firing relies on the intrinsic expression of a variety of CaV and voltage-dependent Na^+ channels in DA neurons as well as HCN channels in the SNc (Neuhoff et al. 2002; Khaliq and Bean 2010). By contrast the transition to bursting requires glutamate release from afferent excitatory inputs and *N*-methyl-D-aspartate (NMDA) receptor activation (Grace et al. 2007; Zweifel et al. 2009). Tonic firing provides background concentrations of extracellular DA, whereas phasic activity drives significantly larger release of DA, necessary to drive motivated behaviors. For example, phasic, but not tonic, DA neurons stimulation is sufficient

to drive conditioned place preference and operant self-stimulation (Tsai et al. 2009; Adamantidis et al. 2011). However, DA neuron inhibition below tonic firing frequencies is also necessary to signal reward prediction error and can be aversive (Schultz 1998; Tan et al. 2012). Therefore, the fine-tuning of DA firing modes allows optimal encoding of external stimuli and adequate behavioral adaptation. Here we review the molecular pathways by which GABA$_B$ receptors in DA neurons modulate overall firing rate, occurrence of bursts and DA release. In other words, we define how GABA$_B$ receptors shape the appropriate responsiveness of DA neurons.

8.3.2 GABA$_B$ Receptor-Mediated Modulation of Firing

8.3.2.1 GIRK Channels

The main effect of somatodendritic GABA$_B$ receptors results from the opening of GIRK channels. The efflux of K^+ hyperpolarizes the membrane and decreases input resistance, all of which elevate the threshold for action potential generation. In slice recordings of SNc, bath-application of baclofen readily hyperpolarizes the membrane potential and decreases firing frequency of both DA and GABA neurons (Lacey et al. 1989). In anesthetized rats, systemic injections of baclofen decrease the firing rate and reduce the occurrence of bursts in VTA and SNc DA neurons, in a dose-dependent manner (Olpe et al. 1977). Local microiontophoresis of baclofen in the VTA yields similar results (Engberg et al. 1993; Erhardt et al. 2002). At low concentrations, this effect is probably mediated in part by activation of presynaptic GABA$_B$ receptors at excitatory terminals onto VTA DA neurons, which display higher coupling efficiency than dendritic receptors in DA neurons. However, the effects of higher concentrations of baclofen are likely to reflect a direct hyperpolarization by DA neuron GABA$_B$ receptors. Supporting this hypothesis, baclofen infusion in the VTA and SNc efficiently decrease DA concentrations in the striatum (Westerink et al. 1992). Similarly, baclofen and saclofen (a GABA$_B$ receptor antagonist) decrease and increase, respectively, DA signals in the NAc, recorded in vivo in awake rats (Xi and Stein 1998). It is therefore likely that somatodendritic GABA$_B$ receptors, by decreasing firing at the cell body, indirectly modulate DA release at the terminals.

8.3.2.2 CaV

Unlike many other neuron types, tonic firing in DA cells heavily relies on external Ca^{2+} and CaV channel opening (Harris et al. 1989). In midbrain DA neurons, GABA$_B$ receptor activation decreases Ca^{2+} currents mediated by high voltage-activated CaV channels such as L-, N-, and P/Q-type (Cardozo and Bean 1995), which were shown to help generate tonic firing (Nedergaard et al. 1993; Puopolo et al. 2007). Therefore it is likely that GABA$_B$ receptor activation also inhibits Ca^{2+} channels, potentially decreasing firing in synergy with GIRK channel opening.

8.3.2.3 HCN

HCN channels, recently identified as members of the extended $GABA_B$ receptor signaling complex, are opened following $GABA_B$ receptor activation and shorten the GIRK channel-mediated hyperpolarization. This repolarization goes physiologically against the grain of all other $GABA_B$ receptor modulations, but may rather provide a passive feedback signal to $GABA_B$ receptors. Additionally, HCN channels sustain tonic firing in SNc DA neurons, where their activation by $GABA_B$ receptors could paradoxically maintain, rather than inhibit, firing, however this question remains to be investigated (Schwenk et al. 2016).

8.3.2.4 NMDA Receptors

Finally, $GABA_B$ receptors can decrease Ca^{2+} current through NMDA receptors in cortical neurons, without affecting the amplitude of NMDA or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor EPSC (Chalifoux and Carter 2010). This effect requires the Gα-mediated inhibition of adenylate cyclase and PKA activity, and is independent of GIRK and CaV channels. The existence of such a mechanism has not yet been investigated in DA neurons, but since bursting requires NMDA receptor activation, this signaling pathway might reduce tonic to phasic firing transitions. Additionally, membrane hyperpolarization through GIRK channels may increase the blockade of NMDAR by Mg^{2+} as suggested in the hippocampus, further decreasing NMDA receptor-mediated transmission (Morrisett et al. 1991; Otmakhova and Lisman 2004). However, it is not clear to which extent Ca^{2+} flowing through NMDA receptors contributes to action potential generation.

8.3.3 $GABA_B$ Receptor-Mediated Modulation of DA Release

DA neurons release DA not only from axons in target regions, but also in the vicinity of their cell body, through somatodendritic vesicular release (Björklund and Lindvall 1975; Geffen et al. 1976; Jaffe et al. 1998). Numerous studies have investigated the mechanisms for these two types of DA release, mostly with fast-scan cycling voltammetry and amperometry measurements of external DA concentrations in slice preparations. These methods take advantage of the unique oxidation/reduction potential of DA to measure rapid variations of external concentration or exocytosis, respectively, with the use of carbon fiber microelectrodes. Overall, in both cases action potential-triggered Ca^{2+} influx through CaV channels seems necessary, although there may be regional or species differences in the source of Ca^{2+} and the exact channels involved (Rice et al. 1997; Ford et al. 2010; Hoffman and Gerhardt 1999; Chen et al. 2006).

8.3.3.1 Dendritic Release

Only a few studies have investigated the effect of GABA$_B$ receptor on somatodendritic DA release. As previously mentioned, postsynaptic GABA$_B$ receptors in DA neurons inhibit CaV channels to modulate firing (Cardozo and Bean 1995). Among these, N-, L-, and T-type channels drive dendritic DA release in the SNc (Beckstead et al. 2004; Kim et al. 2008). Thus, although not directly demonstrated, dendritic GABA$_B$ receptors could inhibit CaV channels and decrease vesicular fusion. Indeed, in vivo local infusion of baclofen nearly abolishes external DA concentrations in the SNc and VTA (Westerink et al. 1992; Santiago et al. 1993b; Klitenick et al. 1992). Conversely, inhibiting GABA$_B$ receptors in SNc slices increases voltammetry DA signals (but not in the VTA, Chen and Rice 2002).

8.3.3.2 Axonal Release

DA axonal release in the dorsal and ventral striatum, emanating from the SNc or VTA DA projections, relies mainly on N- and P/Q-type channels activation, with a potential minor participation of R-type channels (Phillips and Stamford 2000; Chen et al. 2006). All of these channels can be inhibited by GABA$_B$ receptors in different brain regions and cell-types, although this has not been directly demonstrated in DA neurons. Actually, the expression and function of GABA$_B$ receptors in DA neuron terminals remains poorly understood. GABA$_B$ receptor messenger ribonucleic acid (mRNA) autoradiography reveals low expression in the striatum (Kaupmann et al. 1998). Electron microscopy in rats revealed the expression of GABA$_B$ receptors at VGlut2-positive terminals in the striatum, which could belong to either thalamic excitatory neurons or VTA DA neurons (Lacey et al. 2005). In primates, rare presynaptic boutons, displaying the structural features of SNc DA terminals, also express the GABA$_{B1}$ subunit (Charara et al. 2000). At the functional level, microdialysis experiments have shown a lack of, or minimal effect of baclofen infusion in the NAc on DA contents (Santiago et al. 1993a; Westerink et al. 1994; Xi et al. 2003), and a modest decrease or increase of DA in the PFC upon GABA$_B$ receptor activation or antagonization, respectively (Santiago et al. 1993a). A couple of more recent studies, recording electrically evoked DA voltammetry signals in the NAc (Pitman et al. 2014) and dorsal striatum (Schmitz et al. 2002) showed that at saturating concentration, baclofen only blocks 20–40 % of the total signal evoked by single pulses, whereas this number further dropped with increased stimulation frequency stimulation. This is highly divergent from the action of presynaptic GABA$_B$ receptors in most other brain regions and cell types, which usually show high coupling efficiency and almost complete blockade of neurotransmitter release (Lüscher et al. 1997; Padgett et al. 2012). Altogether, these results suggest that GABA$_B$ receptors are present in DA neurons terminals, but assume much less of their traditional function as gatekeepers of release.

The assessment of DA axonal $GABA_B$ receptors modulation of neurotransmitter release has been so far difficult because of the absence of fast, DA-mediated postsynaptic current. However, it was recently discovered that DA neuron subpopulations corelease glutamate (Hnasko et al. 2010) or GABA (Tritsch et al. 2012), as measured by postsynaptic excitatory and inhibitory currents in striatal neurons, respectively. Future studies using these ionotropic responses as readouts for presynaptic regulation of release will hopefully yield more specific insight into the function of presynaptic $GABA_B$ receptors in DA terminals.

8.4 Bidirectional Control of DA Neurons by $GABA_B$ Receptor Agonists

In the VTA, GABA neurons provide a major inhibitory input to DA neurons (Johnson and North 1992a). Inhibition of GABA neurons disinhibits DA neurons, whereas GABA neuron activation shuts DA neurons down, and is sufficient to drive aversive behavioral responses (Tan et al. 2012; van Zessen et al. 2012). Therefore, modulating excitability and release from VTA GABA neurons allows for an indirect, yet powerful handle over DA neuron activity. Here, we review how adequate dosage of $GABA_B$ receptor agonists takes advantage of the VTA microcircuit to bidirectionally modulate DA neuron activity, by selectively inhibiting GABA neurons only or both GABA and DA neurons.

8.4.1 Tailored Agonist Dosage for DA Neuron Disinhibition

As mentioned earlier, VTA GABA neurons express $GABA_B$ receptors and GIRK channels, although with a much higher coupling efficiency than DA neurons, reflected by the ten-fold lower EC50 value for baclofen-mediated GIRK currents in GABA versus DA neurons (Fig. 8.1). In addition, and contrary to DA neurons, axonal $GABA_B$ receptors in GABA neurons strongly modulate synaptic release in the VTA, with an EC50 value for baclofen similar to dendritic receptors (Cruz et al. 2004; Padgett et al. 2012). In other words, there is a window of minimal baclofen concentration (about 0.1 μM) at which dendritic and axonal $GABA_B$ receptors are activated in GABA neurons, but not in DA neurons (Fig. 8.1). Thus, this minimal baclofen concentration inhibits GABA neurons, removes inhibition from GABA to DA neurons and therefore disinhibits DA neurons in slices. Higher concentrations then activate $GABA_B$ receptors in DA neurons, initially normalizing and eventually decreasing DA firing (Cruz et al. 2004).

Interestingly, similar observations were reported with the club drug γ-hydroxybutirate (GHB), a low-affinity $GABA_B$ receptor agonist. As with baclofen, the EC50 value for GIRK currents is one order of magnitude lower in GABA neurons than in DA neurons. Furthermore, saturating concentrations of GHB and baclofen evoke GIRK currents of comparable amplitude in GABA neurons, whereas

GHB yields only 30 % of the maximal baclofen-evoked current in DA neurons. Therefore, a low concentration of GHB, sufficient to activate $GABA_B$ receptors in GABA neurons but without effect in DA neurons, leads to the disinhibition of DA neurons (Labouèbe et al. 2007). For both baclofen and GHB, bidirectional control over DA neuron activity takes advantage of two key features of the VTA: First, the microcircuit formed by GABA neurons' inhibitory innervation of DA neurons, and second, the cell-type-specific coupling efficiency of $GABA_B$ receptor signaling.

8.4.2 Physiological Relevance

These experiments provide a cellular mechanism by which increasing concentrations of $GABA_B$ receptor agonists bidirectionally modulate DA neuron activity. More specifically, at low doses, GABA neuron inhibition leads to the disinhibition of DA neurons and increases DA release throughout the brain, which is the hallmark of addictive drugs (Di Chiara and Imperato 1988). Indeed, GHB is self-administered in rodents (Martellotta et al. 1998) and has abuse potential in humans (Nicholson and Balster 2001) at concentrations leading to DA neuron disinhibition in slices. Similarly, human volunteers engaged in a gambling task show increased reinforcement learning with a low dose of baclofen (compared to a larger dose), presumably through the disinhibition of DA neurons (Terrier et al. 2011).

In contrast, higher concentrations of baclofen or GHB decrease DA neuron activity and DA release, by hyperpolarizing the membrane and increasing the threshold for burst firing. Moreover, agonist concentrations sufficient to activate $GABA_B$ receptors in DA neurons are also likely to activate high coupling efficiency presynaptic receptors at excitatory inputs, decreasing glutamate release (Padgett et al. 2012). Accordingly, baclofen infusion in the VTA of rodents reduces self-administration of various addictive drugs (Shoaib et al. 1998; Xi and Stein 2000; Corrigall et al. 2000; see also Chaps. 14 and 15 of this book). Baclofen is also used in humans as an anticraving agent for addictive drugs like cocaine and alcohol (Ling et al. 1998; Ameisen 2005; Addolorato et al. 2009; see also Chaps. 14 and 15 of this book), an effect occasionally observed with GHB itself (Gallimberti et al. 1989).

8.5 Plasticity of $GABA_B$ Receptor Signaling

While most studies on synaptic plasticity examine excitatory transmission, various forms of plasticity of $GABA_A$ receptor-mediated transmission have been identified (Castillo et al. 2011; Kullmann et al. 2012). Only a handful of studies have characterized activity-dependent and drug-evoked plasticity of $GABA_B$ receptor signaling. Here we review these observations with an emphasis on those occurring in the mesolimbic circuit, and discuss their induction and expression mechanisms as well as their functional implications.

8.5.1 *Activity-Dependent Plasticity*

8.5.1.1 Induction

The induction of all forms of activity-dependent $GABA_B$ receptor signaling plasticity described so far requires NMDA receptor activation. Various induction protocols, like electrical stimulation of glutamate release and postsynaptic membrane depolarization in slices, or bath application of NMDA receptor agonists in cell cultures, lead to potentiation or depression of $GABA_B$ receptor signaling. The direction of the plasticity is then specified by distinct expression mechanisms.

8.5.1.2 Potentiation

The first electrophysiological study to report activity-dependent synaptic plasticity of $GABA_B$ receptors in cell cultures and acute hippocampal slices showed that a classic AMPA receptor long-term potentiation protocol potentiates $GABA_B$ receptor-mediated IPSCs. The induction requires electrical stimulation of synaptic glutamate release paired with postsynaptic membrane depolarization, which activates NMDA receptors, increases intracellular Ca^{2+}, and recruits Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII; Huang et al. 2005). Similar induction mechanism was recently observed in VTA DA neurons, in which sustained depolarization or burst firing leads to the potentiation of $GABA_B$ receptor-GIRK currents (Lalive et al. 2014). Blocking the trafficking of GIRK channels by interfering specifically with PDZ-binding domains on GIRK2c or GIRK3 prevents the potentiation of $GABA_B$ receptor-GIRK currents in DA neurons, suggesting that $GABA_B$-GIRK plasticity is expressed through surface delivery of heteromeric GIRK2c/3 channels in DA neurons (Fig. 8.2). Expression mechanisms in the hippocampus could additionally involve protein phosphatase (PP) 1-dependent phosphorylation of Serine (S) 9 residue on GIRK2 to modulate channel trafficking (Chung et al. 2009). Lastly, NMDA application transiently increases $GABA_B$ receptor surface expression by recruiting 5′-adenosine monophosphate-activated kinase (AMPK)-mediated phosphorylation at S783 on the $GABA_{B2}$ subunit in cortical neuron cultures (Terunuma et al. 2010). A similar increase was also reported following glycine-mediated synaptic NMDA receptor activation, which was prevented by inhibiting protein recycling (Kantamneni et al. 2014).

8.5.1.3 Depression

In cultured hippocampal neurons, prolonged (30 min) NMDA receptor activation induces a Ca^{2+}- and CaMKII-dependent depression of $GABA_B$ receptor signaling. CaMKII specifically phosphorylates S892 on $GABA_{B1b}$, which drives the internalization of $GABA_B$ receptors (Guetg et al. 2010). In cultured cortical neurons, a similar induction protocol depresses baclofen-evoked currents. The exact induction mechanism is not identified, however expression requires increased PP2 activity

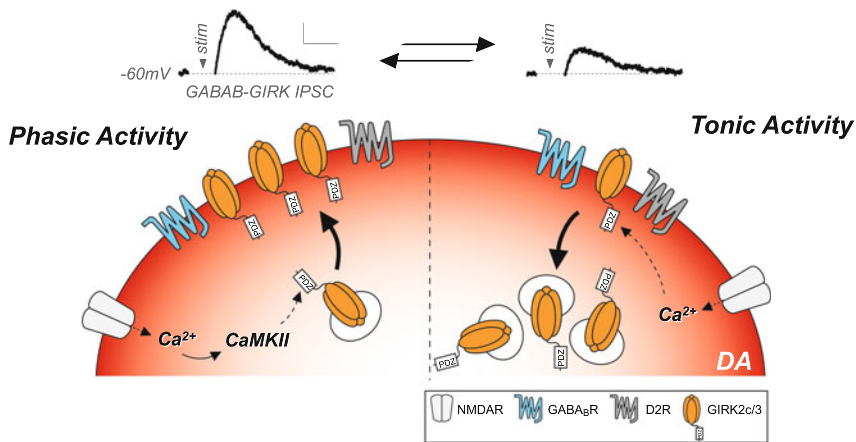

Fig. 8.2 Dopamine neuron firing drives bidirectional GIRK channel plasticity. (*Left*) NMDA receptor and phasic activity drive Ca^{2+} entry and CaMKII activation, engaging a molecular pathway interacting with GIRK2c/3 PDZ domain and trafficking channels at the membrane. This results in the potentiation of GABA$_B$ and D2 receptor-GIRK currents, illustrated by the example recording of a large GABA$_B$ receptor-GIRK IPSC, evoked by electrical stimulation at −60 mV (*top inset*). (*Right*) Tonic activity or tonic NMDA receptor activation drives Ca^{2+} entry, triggering an undetermined molecular cascade eventually driving the internalization of GIRK2c/3 channels through a PDZ domain interaction, resulting in the depression of GABA$_B$ and potentially D2 receptor-GIRK currents, as shown by the reduced amplitude of electrically evoked GABA$_B$ receptor-GIRK IPSC (*top inset*). Scale: 20pA, 200 ms [*Inset* traces reproduced from Lalive et al. 2014]

and dephosphorylation of GABA$_{B2}$ S783, leading to decreased surface expression of GABA$_B$ receptors (Terunuma et al. 2010). It appears that dephosphorylation of GABA$_{B2}$ does not directly trigger the internalization of the receptor, but rather modifies basal recycling at the level of postendocytic sorting. This mechanism has since been implicated in GABA$_B$ receptor plasticity in VTA GABA neurons and PFC (Padgett et al. 2012; Hearing et al. 2013) (further described in the drug-evoked plasticity section below), and in the lateral habenula following exposure to aversive stimuli (Lecca et al. 2016), suggesting a crucial and widely distributed plasticity mechanism. In VTA DA neurons, low frequency tonic firing or synaptic activation of NMDA receptors for 5 min decreases the amplitude of GABA$_B$ receptor-GIRK IPSC (Fig. 8.2). Similarly to the burst-induced potentiation, this plasticity is expressed by trafficking of GIRK3-containing channels (Lalive et al. 2014).

8.5.1.4 Functional Significance

Overall, GABA$_B$ receptor plasticity seems tightly tuned to neuronal excitation. It is striking that all of the above-described mechanisms rely on excitatory input stimulation for their induction. This may then lead to NMDA receptor activation

or action potential firing, suggesting that plasticity of $GABA_B$ receptor signaling is an adaptive response to changes in neuronal activity (Fig. 8.2). A unifying interpretation would suggest that this inhibitory plasticity is called in as a compensatory, homeostatic-like adaption, where $GABA_B$ receptor function is potentiated following sustained activity, but reduced after periods of little activity. This hypothesis is especially supported in VTA DA neurons, where GIRK channel upregulation is functionally not restricted to $GABA_B$ receptors, but also potentiates Dopamine 2 receptor-GIRK currents, thereby strengthening another inhibitory pathway (Lalive et al. 2014). Overall, $GABA_B$ receptor plasticity further emphasizes the second-order nature of $GABA_B$ receptor function in tempering neuronal excitability and responsiveness to relevant synaptic signals.

8.5.2 Drug-Evoked Plasticity of $GABA_B$ Receptor Signaling

A hallmark of addictive drugs is the induction of excitatory synaptic plasticity in VTA DA neurons after a single exposure, which eventually spreads to other nuclei following repeated intake or withdrawal periods and underlies the development of addictive behaviors (Lüscher and Malenka 2011). Similarly, drugs of abuse evoke various forms of $GABA_B$ receptor signaling plasticity (Table 8.2), however their functional significance is debated.

8.5.2.1 Early Observations

Early work revealed a decrease in $G\alpha_{i/o}$ protein in the VTA and NAc following chronic but not acute cocaine treatment in rats, hinting at metabotropic signaling alterations (Nestler et al. 1990). Similar results were later obtained after withdrawal from chronic psychostimulants (Zhang et al. 2000; Xi et al. 2003; Giorgetti et al. 2002). Additionally, most GIRK knockout mice show altered drug-related behavior (Luján et al. 2014). Altogether these results pointed early on toward a potential modulation of $GABA_B$ receptor signaling following exposure to drugs of abuse. Unfortunately the techniques employed in these studies do not allow the distinction between neuron types and axonal from dendritic $GABA_B$ receptors, blurring functional interpretation. Patch-clamp studies in identified cell types have then helped overcome these confounds and shed light on the molecular mechanisms underlying drug-evoked plasticity of $GABA_B$ receptor signaling.

8.5.2.2 Plasticity in VTA Neurons

A single exposure to psychostimulants like cocaine and methamphetamine is sufficient to evoke a decrease in $GABA_B$ receptor-GIRK currents in VTA DA and GABA neurons (Padgett et al. 2012; Arora et al. 2011). This adaptation is also observed in DA neurons

Table 8.2 Summary of $GABA_B$ receptor signaling plasticity in the VTA

	Cell-type	Plasticity	Protocol	Induction	Expression
Activity-dependent	DA	Potentiation (IPSC and baclofen)	Depolarization, burst firing	NMDAR	GIRK2c/3 trafficking
				Ca^{2+}	Lalive et al. (2014)
				CaMKII	
	DA	Depression (IPSC)	Tonic firing	NMDAR	GIRK2c/3 trafficking
					Lalive et al. (2014)
Drug-evoked	DA	Depression (baclofen, but IPSC unchanged)	Cocaine, meth (1–5 days)	D1R, D2R	GIRK channel internalization
		Self-administration (14 days)			Arora et al. (2011), Munoz et al. (2016), and Sharpe et al. (2015)
	DA	Increased coupling efficiency	Morphine, GHB (5 days)	?	RGS2 downregulation
					Labouèbe et al. (2007)
	GABA	Depression (IPSC, baclofen)	Cocaine, meth (1 day)	D1R	PP2A dephosphorylation of GABAB2 S783; GABABR-GIRK internalization
					Padgett et al. (2012)
	VTA-projecting PFC	Depression (baclofen, somatodendritic)	Cocaine (5 days)	D1R	PP2A dephosphorylation of GABAB2 S783; GABABR-GIRK internalization
					Hearing et al. (2013)
	Excitatory inputs to DA	Increased coupling efficiency (axonal)	Morphine (6 days)	?	?
					Manzoni and Williams (1999)

after repeated passive injections (Munoz et al. 2016) or active self-administration of psychostimulants (Sharpe et al. 2015). In both cell types, plasticity induction requires DA type 1 (D1) and DA type 2 (D2) receptor activation, however the molecular pathways underlying plasticity expression are highly different.

In DA neurons, the reduction in $GABA_B$ receptor signaling is mediated by a decrease in GIRK channel density (but not $GABA_B$ receptors) at the membrane (Arora et al. 2011). Interestingly, in DA neurons lacking the GIRK3 subunit, psychostimulants fail to depress baclofen-evoked currents, suggesting that trafficking of GIRK2c/3 heteromers is required (Munoz et al. 2016), similar to activity-dependent GIRK plasticity described in the same cells (Lalive et al. 2014). Additionally, DA neurons lacking SNX27 display blunted baclofen-evoked currents (Munoz and Slesinger 2014). SNX27 is involved in trafficking of GIRK2c/3 channels and is sensitive to drugs of abuse (Kajii et al. 2003), and may therefore participate to $GABA_B$ receptor signaling plasticity in DA neurons.

In GABA neurons, the decrease in $GABA_B$ receptor signaling is also observed in axon terminals, where the coupling efficiency is reduced (Padgett et al. 2012). The reduction in $GABA_B$ receptor-GIRK currents is due to enhanced PP2A-mediated dephosphorylation of $GABA_{B2}$ S783, a pathway previously identified for activity-dependent depression of $GABA_B$ receptor signaling (Terunuma et al. 2010). As a result, $GABA_B$ receptors and GIRK channels are internalized but not degraded, and acute PP2A inhibition rescues the full amplitude of baclofen-evoked currents. Furthermore, this plasticity is blocked in a mouse expressing a $GABA_{B2}$ subunit insensitive to PP2A dephosphorylation (Munoz et al. 2016). Interestingly, GIRK channels do not interact with PP2A but are also removed from the membrane, possibly because of their proximity to $GABA_B$ receptors (Padgett et al. 2012).

Drugs other than psychostimulants also evoke $GABA_B$ receptor signaling plasticity. Chronic GHB or morphine treatment increases the coupling efficiency of $GABA_B$ receptors to GIRK channels in VTA DA neurons. This specific effect is mediated by the downregulation of RGS2, a protein acting as a brake on G protein signaling. Consistent with this, the coupling efficiency is increased in RGS2 knockout mice, and drug treatment has no further effect (Labouèbe et al. 2007).

8.5.2.3 Plasticity of VTA Afferents

In VTA-projecting PFC neurons, repeated cocaine injection decreases baclofen-evoked currents in a D1 receptor-dependent fashion (Hearing et al. 2013). $GABA_B$ receptors are internalized following PP2A-dependent S783 GABAB2 dephosphorylation, similar to what was described in VTA GABA neurons (Padgett et al. 2012). It is not known whether $GABA_B$ receptor signaling is also altered in axons projecting to the VTA. Interestingly, chronic morphine increases the coupling efficiency of presynaptic $GABA_B$ receptors at excitatory terminals onto DA neurons (Manzoni and Williams 1999). However, this was observed with nonspecific electrical stimulation and may not reflect $GABA_B$ receptor function at all axon terminals.

8.5.2.4 Functional Significance

In DA neurons, the reduction in maximal baclofen-evoked current after psychostimulant exposure is paralleled with a mild decrease in the ability of $GABA_B$ receptors to block neuronal activity (Munoz et al. 2016). In other words, DA neurons are partially relieved from the rule of $GABA_B$ receptors. However, in the same conditions synaptically evoked $GABA_B$ receptor GIRK IPSCs, which reflect a more physiological mode of $GABA_B$ receptor activation, are unaffected (Padgett et al. 2012). This suggests that despite GIRK channel internalization, $GABA_B$ receptor signaling is still fully functional under physiological levels of activation. In stark contrast, synaptically evoked $GABA_B$ receptor-GIRK IPSC in VTA GABA neurons are absent following drug exposure, arguing for a physiologically relevant functional deficiency. Accordingly, $GABA_B$ receptor activation, even with saturating concentrations of baclofen, is unable to decrease firing (Padgett et al. 2012). Therefore, the VTA microcircuit is altered: GABA neuron activity is less likely to be inhibited, and its inhibitory control over DA neurons may be strengthened. Similarly, the increase in coupling efficiency in DA neurons after morphine treatment empowers $GABA_B$ receptors to modulate DA neuron excitability. Indeed, DA neurons are now inhibited by a minimal concentration of baclofen (0.1 μM) that would only affect GABA neurons in control conditions (Labouèbe et al. 2007). To fully predict the net functional effect of these forms of plasticity, two key questions need to be answered. First of all, do these plasticities represent a uniform and simultaneous adaptation following exposure to any drug of abuse, like it has been suggested for excitatory plasticity (Lüscher and Ungless 2006), or are they tailor-cut to specific drugs? For example, a decrease in $GABA_B$ receptor GIRK current amplitude in DA neurons, as seen after psychostimulant exposure (Arora et al. 2011), might be compensated for by an increase in coupling efficiency, as observed after morphine treatment (Labouèbe et al. 2007), resulting in no functional difference. Second, what is the actual concentration of endogenous agonist to which $GABA_B$ receptors are exposed in vivo? In other words, thus far it has been difficult to infer the physiological function of $GABA_B$ receptors from maximal baclofen-evoked current amplitude.

8.5.2.5 Drug-Evoked Plasticity: Compensatory or Contributory?

Drug-evoked excitatory synaptic plasticity is believed to progressively modify circuit function and eventually lead to the development of addictive behaviors (Lüscher and Malenka 2011). Repeated drug exposure increases DA neuron activity and excitability (White 1996; Henry et al. 1989). However, it is not clear whether $GABA_B$ receptor signaling plasticity subserves or counteracts these circuit changes. The loss of $GABA_B$ receptor function in VTA GABA neurons argues for a compensatory mechanism, promoting GABA release onto DA neurons to limit their activity (Padgett et al. 2012). However, mimicking the drug-evoked plasticity by downregulating GIRK channels in VTA DA neurons or PFC increases the acute locomotor response to psychostimulant, suggesting an active participation to the behavioral effects of addictive drugs (Munoz and Slesinger 2014; Hearing et al. 2013).

Over recent years $GABA_B$ receptor plasticity has emerged as a cellular mechanism relevant to neuronal activity and circuit function. Activity-dependent and drug-evoked adaptations occur in different cell types and regions, concurrently with excitatory plasticity. Whereas excitatory synaptic plasticity is usually perceived as the primary neural correlate of experience, $GABA_B$ receptor plasticity rather appears as a secondary adaptation that may either stabilize or derail neuronal excitability, especially in DA neurons. Future studies will have to causally assess the contribution of $GABA_B$ receptor signaling plasticity to neuronal activity and behavioral alterations in the context of addiction disease.

8.6 Conclusions

$GABA_B$ receptors engage diverse signaling pathways to hyperpolarize somatodendritic compartments and reduce probability of neurotransmitter release, thus exerting a pre- and postsynaptic modulation of neural activity. In the VTA, the cell-type-specific composition of $GABA_B$ receptor complexes determines the signaling efficacy and allows for bidirectional control of DA output through inhibition of local interneurons. $GABA_B$ receptor agonists may thus lead to disinihibition at low concentration, while inhibiting DA neurons at higher doses. This may explain the reinforcing effects of baclofen and GHB and associated risk for addiction. This model also accounts for the anti-craving effect of high doses of baclofen.

In DA neurons, where dynamic switching between pauses, tonic, and phasic firing occurs with experience, $GABA_B$ receptors control the excitability and adjust responsiveness to relevant synaptic inputs. Furthermore, $GABA_B$ receptor signaling can undergo plasticity and adapts to changes in neuronal activity, which may constitute a compensatory mechanism to maintain physiological neuronal activity. Addictive drugs also alter $GABA_B$ receptor signaling throughout the mesolimbic system, however the relevance of this plasticity for the development of addictive behavior remains elusive.

Altogether, $GABA_B$ receptors are effective and dynamic modulators of the DA system, and form a target with potential for pharmacological interventions in humans.

Acknowledgments We thank Tony Lien for comments on the manuscript. A.L.L. and C.L. are supported by grants from the Swiss National Science Foundation.

References

Adamantidis, A. R., Tsai, H.-C., Boutrel, B., Zhang, F., Stuber, G. D., Budygin, E. A., et al. (2011). Optogenetic interrogation of dopaminergic modulation of the multiple phases of reward-seeking behavior. *The Journal of Neuroscience, 31*, 10829–10835.

Addolorato, G., Leggio, L., Cardone, S., Ferrulli, A., & Gasbarrini, G. (2009). Role of the GABA(B) receptor system in alcoholism and stress: Focus on clinical studies and treatment perspectives. *Alcohol (Fayetteville, NY), 43*, 559–563.

Ameisen, O. (2005). Complete and prolonged suppression of symptoms and consequences of alcohol-dependence using high-dose baclofen: A self-case report of a physician. *Alcohol and Alcoholism (Oxford, Oxfordshire), 40*, 147–150.

Arora, D., Haluk, D. M., Kourrich, S., Pravetoni, M., Fernández-Alacid, L., Nicolau, J. C., et al. (2010). Altered neurotransmission in the mesolimbic reward system of Girk mice. *Journal of Neurochemistry, 114*, 1487–1497.

Arora, D., Hearing, M., Haluk, D. M., Mirkovic, K., Fajardo-Serrano, A., Wessendorf, M. W., et al. (2011). Acute cocaine exposure weakens GABAB receptor-dependent G-protein-gated inwardly rectifying K+ signaling in dopamine neurons of the ventral tegmental area. *The Journal of Neuroscience, 31*, 12251–12257.

Balana, B., Bahima, L., Bodhinathan, K., Taura, J. J., Taylor, N. M., Nettleton, M. Y., et al. (2013). Ras-association domain of sorting Nexin 27 is critical for regulating expression of GIRK potassium channels. *PLoS One, 8*, e59800.

Beckstead, M. J., Grandy, D. K., Wickman, K., & Williams, J. T. (2004). Vesicular dopamine release elicits an inhibitory postsynaptic current in midbrain dopamine neurons. *Neuron, 42*, 939–946.

Beier, K. T., Steinberg, E. E., DeLoach, K. E., Xie, S., Miyamichi, K., Schwarz, L., et al. (2015). Circuit architecture of VTA dopamine neurons revealed by systematic input-output mapping. *Cell, 162*, 622–634.

Bettler, B., Kaupmann, K., Mosbacher, J., & Gassmann, M. (2004). Molecular structure and physiological functions of GABA(B) receptors. *Physiological Reviews, 84*, 835–867.

Björklund, A., & Lindvall, O. (1975). Dopamine in dendrites of substantia nigra neurons: Suggestions for a role in dendritic terminals. *Brain Research, 83*, 531–537.

Bocklisch, C., Pascoli, V., Wong, J. C. Y., House, D. R. C., Yvon, C., De Roo, M., et al. (2013). Cocaine disinhibits dopamine neurons by potentiation of GABA transmission in the ventral tegmental area. *Science, 341*, 1521–1525.

Boyes, J., & Bolam, J. P. (2003). The subcellular localization of GABA(B) receptor subunits in the rat substantia nigra. *The European Journal of Neuroscience, 18*, 3279–3293.

Brazhnik, E., Shah, F., & Tepper, J. M. (2008). GABAergic afferents activate both GABAA and GABAB receptors in mouse substantia nigra dopaminergic neurons in vivo. *The Journal of Neuroscience, 28*, 10386–10398.

Cameron, D. L., & Williams, J. T. (1993). Dopamine D1 receptors facilitate transmitter release. *Nature, 366*, 344–347.

Cardozo, D. L., & Bean, B. P. (1995). Voltage-dependent calcium channels in rat midbrain dopamine neurons: Modulation by dopamine and GABAB receptors. *Journal of Neurophysiology, 74*, 1137–1148.

Castillo, P. E., Chiu, C. Q., & Carroll, R. C. (2011). Long-term plasticity at inhibitory synapses. *Current Opinion in Neurobiology, 21*, 328–338.

Chalifoux, J. R., & Carter, A. G. (2010). GABAB receptors modulate NMDA receptor calcium signals in dendritic spines. *Neuron, 66*, 101–113.

Charara, A., Heilman, T. C., Levey, A. I., & Smith, Y. (2000). Pre- and postsynaptic localization of GABA(B) receptors in the basal ganglia in monkeys. *Neuroscience, 95*, 127–140.

Chen, B. T., Moran, K. A., Avshalumov, M. V., & Rice, M. E. (2006). Limited regulation of somatodendritic dopamine release by voltage-sensitive Ca channels contrasted with strong regulation of axonal dopamine release. *Journal of Neurochemistry, 96*, 645–655.

Chen, B. T., & Rice, M. E. (2002). Synaptic regulation of somatodendritic dopamine release by glutamate and GABA differs between substantia nigra and ventral tegmental area. *Journal of Neurochemistry, 81*, 158–169.

Chung, H. J., Qian, X., Ehlers, M., Jan, Y. N., & Jan, L. Y. (2009). Neuronal activity regulates phosphorylation-dependent surface delivery of G protein-activated inwardly rectifying potassium channels. *Proceedings of the National Academy of Sciences of the United States of America, 106*, 629–634.

Ciruela, F., Fernández-Dueñas, V., Sahlholm, K., Fernández-Alacid, L., Nicolau, J. C., Watanabe, M., et al. (2010). Evidence for oligomerization between GABA(B) receptors and GIRK channels containing the GIRK1 and GIRK3 subunits. *The European Journal of Neuroscience, 32*(8), 1265–1277.

Corrigall, W. A., Coen, K. M., Adamson, K. L., Chow, B. L., & Zhang, J. (2000). Response of nicotine self-administration in the rat to manipulations of mu-opioid and gamma-aminobutyric acid receptors in the ventral tegmental area. *Psychopharmacology, 149*, 107–114.

Couve, A., Thomas, P., Calver, A. R., Hirst, W. D., Pangalos, M. N., Walsh, F. S., et al. (2002). Cyclic AMP-dependent protein kinase phosphorylation facilitates GABA(B) receptor-effector coupling. *Nature Neuroscience, 5*, 415–424.

Cruz, H. G., Ivanova, T., Lunn, M.-L., Stoffel, M., Slesinger, P. A., & Lüscher, C. (2004). Bi-directional effects of GABA(B) receptor agonists on the mesolimbic dopamine system. *Nature Neuroscience, 7*, 153–159.

David, M., Richer, M., Mamarbachi, A. M., Villeneuve, L. R., Dupré, D. J., & Hebert, T. E. (2006). Interactions between GABA-B1 receptors and Kir 3 inwardly rectifying potassium channels. *Cellular Signalling, 18*, 2172–2181.

Di Chiara, G., & Imperato, A. (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Sciences of the United States of America, 85*, 5274–5278.

Dobi, A., Margolis, E. B., Wang, H.-L., Harvey, B. K., & Morales, M. (2010). Glutamatergic and nonglutamatergic neurons of the ventral tegmental area establish local synaptic contacts with dopaminergic and nondopaminergic neurons. *The Journal of Neuroscience, 30*, 218–229.

Doupnik, C. A., Jaén, C., & Zhang, Q. (2004) *Measuring the modulatory effects of RGS proteins on GIRK channels* (pp 131–154). Department of Physiology and Biophysics, University of South Florida College of Medicine. Tampa: Elsevier.

Engberg, G., Kling-Petersen, T., & Nissbrandt, H. (1993). GABAB-receptor activation alters the firing pattern of dopamine neurons in the rat substantia nigra. *Synapse (New York, NY), 15*, 229–238.

Erhardt, S., Mathé, J. M., Chergui, K., Engberg, G., & Svensson, T. H. (2002). GABA(B) receptor-mediated modulation of the firing pattern of ventral tegmental area dopamine neurons in vivo. *Naunyn-Schmiedeberg's Archives of Pharmacology, 365*, 173–180.

Ford, C. P., Gantz, S. C., Phillips, P. E. M., & Williams, J. T. (2010). Control of extracellular dopamine at dendrite and axon terminals. *The Journal of Neuroscience, 30*, 6975–6983.

Fowler, C. E., Aryal, P., Suen, K.-F., & Slesinger, P. A. (2007). Evidence for association of GABAB receptors with Kir3 channels and regulators of G protein signalling (RGS4) proteins. *The Journal of Physiology, 580*, 51–65.

Gallimberti, L., Canton, G., Gentile, N., Ferri, M., Cibin, M., Ferrara, S. D., et al. (1989). Gamma-hydroxybutyric acid for treatment of alcohol withdrawal syndrome. *Lancet (London, England), 2*, 787–789.

Geffen, L. B., Jessell, T. M., Cuello, A. C., & Iversen, L. L. (1976). Release of dopamine from dendrites in rat substantia nigra. *Nature, 260*, 258–260.

Giorgetti, M., Hotsenpiller, G., Froestl, W., & Wolf, M. E. (2002). In vivo modulation of ventral tegmental area dopamine and glutamate efflux by local GABA(B) receptors is altered after repeated amphetamine treatment. *Neuroscience, 109*, 585–595.

Grace, A. A., & Bunney, B. S. (1984a). The control of firing pattern in nigral dopamine neurons: Burst firing. *The Journal of Neuroscience, 4*, 2877–2890.

Grace, A. A., & Bunney, B. S. (1984b). The control of firing pattern in nigral dopamine neurons: Single spike firing. *The Journal of Neuroscience, 4*, 2866–2876.

Grace, A. A., Floresco, S. B., Goto, Y., & Lodge, D. J. (2007). Regulation of firing of dopaminergic neurons and control of goal-directed behaviors. *Trends in Neurosciences, 30*, 220–227.

Guetg, N., Abdel Aziz, S., Holbro, N., Turecek, R., Rose, T., Seddik, R., et al. (2010). NMDA receptor-dependent GABAB receptor internalization via CaMKII phosphorylation of serine 867 in GABAB1. *Proceedings of the National Academy of Sciences of the United States of America, 107*(31), 13924–13929.

Harris, N. C., Webb, C., & Greenfield, S. A. (1989). A possible pacemaker mechanism in pars compacta neurons of the guinea-pig substantia nigra revealed by various ion channel blocking agents. *Neuroscience, 31*, 355–362.

Hearing, M., Kotecki, L., Marron Fernandez de Velasco, E., Fajardo-Serrano, A., Chung, H. J., Luján, R., et al. (2013). Repeated cocaine weakens GABAB-Girk signaling in layer 5/6 pyramidal neurons in the prelimbic cortex. *Neuron, 80*, 159–170.

Henry, D. J., Greene, M. A., & White, F. J. (1989). Electrophysiological effects of cocaine in the mesoaccumbens dopamine system: Repeated administration. *The Journal of Pharmacology and Experimental Therapeutics, 251*, 833–839.

Hnasko, T. S., Chuhma, N., Zhang, H., Goh, G. Y., Sulzer, D., Palmiter, R. D., et al. (2010). Vesicular glutamate transport promotes dopamine storage and glutamate corelease in vivo. *Neuron, 65*, 643–656.

Hoffman, A. F., & Gerhardt, G. A. (1999). Differences in pharmacological properties of dopamine release between the substantia nigra and striatum: An in vivo electrochemical study. *The Journal of Pharmacology and Experimental Therapeutics, 289*, 455–463.

Huang, C. S., Shi, S.-H., Ule, J., Ruggiu, M., Barker, L. A., Darnell, R. B., et al. (2005). Common molecular pathways mediate long-term potentiation of synaptic excitation and slow synaptic inhibition. *Cell, 123*, 105–118.

Inanobe, A., Yoshimoto, Y., Horio, Y., Morishige, K. I., Hibino, H., Matsumoto, S., et al. (1999). Characterization of G-protein-gated K+ channels composed of Kir3.2 subunits in dopaminergic neurons of the substantia nigra. *The Journal of Neuroscience, 19*, 1006–1017.

Jaffe, E. H., Marty, A., Schulte, A., & Chow, R. H. (1998). Extrasynaptic vesicular transmitter release from the somata of substantia nigra neurons in rat midbrain slices. *The Journal of Neuroscience, 18*, 3548–3553.

Johnson, S. W., & North, R. A. (1992a). Opioids excite dopamine neurons by hyperpolarization of local interneurons. *The Journal of Neuroscience, 12*, 483–488.

Johnson, S. W., & North, R. A. (1992b). Two types of neurone in the rat ventral tegmental area and their synaptic inputs. *The Journal of Physiology, 450*, 455–468.

Jones, K. A., Borowsky, B., Tamm, J. A., Craig, D. A., Durkin, M. M., Dai, M., et al. (1998). GABA(B) receptors function as a heteromeric assembly of the subunits GABA(B)R1 and GABA(B)R2. *Nature, 396*, 674–679.

Joubert, L., Hanson, B., Barthet, G., Sebben, M., Claeysen, S., Hong, W., et al. (2004). New sorting nexin (SNX27) and NHERF specifically interact with the 5-HT4a receptor splice variant: Roles in receptor targeting. *Journal of Cell Science, 117*, 5367–5379.

Kajii, Y., Muraoka, S., Hiraoka, S., Fujiyama, K., Umino, A., & Nishikawa, T. (2003). A developmentally regulated and psychostimulant-inducible novel rat gene mrt1 encoding PDZ-PX proteins isolated in the neocortex. *Molecular Psychiatry, 8*, 434–444.

Kantamneni, S., Gonzàlez-Gonzàlez, I. M., Luo, J., Cimarosti, H., Jacobs, S. C., Jaafari, N., et al. (2014). Differential regulation of GABAB receptor trafficking by different modes of N-methyl-D-aspartate (NMDA) receptor signaling. *The Journal of Biological Chemistry, 289*, 6681–6694.

Kaupmann, K., Malitschek, B., Schuler, V., Heid, J., Froestl, W., Beck, P., et al. (1998). GABA(B)-receptor subtypes assemble into functional heteromeric complexes. *Nature, 396*, 683–687.

Khaliq, Z. M., & Bean, B. P. (2010). Pacemaking in dopaminergic ventral tegmental area neurons: Depolarizing drive from background and voltage-dependent sodium conductances. *The Journal of Neuroscience, 30*, 7401–7413.

Kim, Y., Park, M. K., & Chung, S. (2008). Voltage-operated Ca^{2+} channels regulate dopamine release from somata of dopamine neurons in the substantia nigra pars compacta. *Biochemical and Biophysical Research Communications, 373*, 665–669.

Klitenick, M. A., DeWitte, P., & Kalivas, P. W. (1992). Regulation of somatodendritic dopamine release in the ventral tegmental area by opioids and GABA: An in vivo microdialysis study. *The Journal of Neuroscience, 12*, 2623–2632.

Koyrakh, L., Luján, R., Colón, J., Karschin, C., Kurachi, Y., Karschin, A., et al. (2005). Molecular and cellular diversity of neuronal G-protein-gated potassium channels. *The Journal of Neuroscience, 25*, 11468–11478.

Kullmann, D. M., Moreau, A. W., Bakiri, Y., & Nicholson, E. (2012). Plasticity of inhibition. *Neuron, 75*, 951–962.

Labouèbe, G., Lomazzi, M., Cruz, H. G., Creton, C., Luján, R., Li, M., et al. (2007). RGS2 modulates coupling between GABAB receptors and GIRK channels in dopamine neurons of the ventral tegmental area. *Nature Neuroscience, 10*, 1559–1568.

Lacey, C. J., Boyes, J., Gerlach, O., Chen, L., Magill, P. J., & Bolam, J. P. (2005). GABA(B) receptors at glutamatergic synapses in the rat striatum. *Neuroscience, 136*, 1083–1095.

Lacey, M. G., Mercuri, N. B., & North, R. A. (1989). Two cell types in rat substantia nigra zona compacta distinguished by membrane properties and the actions of dopamine and opioids. *The Journal of Neuroscience, 9*, 1233–1241.

Lalive, A. L., Munoz, M. B., Bellone, C., Slesinger, P. A., Lüscher, C., & Tan, K. R. (2014). Firing modes of dopamine neurons drive bidirectional GIRK channel plasticity. *The Journal of Neuroscience, 34*, 5107–5114.

Lauffer, B. E. L., Melero, C., Temkin, P., Lei, C., Hong, W., Kortemme, T., et al. (2010). SNX27 mediates PDZ-directed sorting from endosomes to the plasma membrane. *The Journal of Cell Biology, 190*, 565–574.

Lecca, S., Pelosi, A., Tchenio, A., Moutkine, I., Luján, R., Hervé, D., et al. (2016). Rescue of GABAB and GIRK function in the lateral habenula by protein phosphatase 2A inhibition ameliorates depression-like phenotypes in mice. *Nature Medicine, 22*, 254–261.

Ling, W., Shoptaw, S., & Majewska, D. (1998). Baclofen as a cocaine anti-craving medication: A preliminary clinical study. *Neuropsychopharmacology, 18*, 403–404.

Luján, R., Marron Fernandez de Velasco, E., Aguado, C., & Wickman, K. (2014). New insights into the therapeutic potential of Girk channels. *Trends in Neurosciences, 37*, 20–29.

Lunn, M.-L., Nassirpour, R., Arrabit, C., Tan, J., McLeod, I., Arias, C. M., et al. (2007). A unique sorting nexin regulates trafficking of potassium channels via a PDZ domain interaction. *Nature Neuroscience, 10*, 1249–1259.

Lüscher, C., Jan, L. Y., Stoffel, M., Malenka, R. C., & Nicoll, R. A. (1997). G protein-coupled inwardly rectifying K+ channels (GIRKs) mediate postsynaptic but not presynaptic transmitter actions in hippocampal neurons. *Neuron, 19*, 687–695.

Lüscher, C., & Malenka, R. C. (2011). Drug-evoked synaptic plasticity in addiction: From molecular changes to circuit remodeling. *Neuron, 69*, 650–663.

Lüscher, C., & Slesinger, P. A. (2010). Emerging roles for G protein-gated inwardly rectifying potassium (GIRK) channels in health and disease. *Nature Reviews Neuroscience, 11*(5), 301–315.

Lüscher, C., & Ungless, M. A. (2006). The mechanistic classification of addictive drugs. *PLoS Medicine, 3*, e437.

Manzoni, O. J., & Williams, J. T. (1999). Presynaptic regulation of glutamate release in the ventral tegmental area during morphine withdrawal. *The Journal of Neuroscience, 19*, 6629–6636.

Martellotta, M. C., Cossu, G., Fattore, L., Gessa, G. L., & Fratta, W. (1998). Intravenous self-administration of gamma-hydroxybutyric acid in drug-naive mice. *European Neuropsychophar macology, 8*, 293–296.

Metz, M., Gassmann, M., Fakler, B., Schaeren-Wiemers, N., & Bettler, B. (2011). Distribution of the auxiliary GABAB receptor subunits KCTD8, 12, 12b, and 16 in the mouse brain. *The Journal of Comparative Neurology, 519*, 1435–1454.

Morrisett, R. A., Mott, D. D., Lewis, D. V., Swartzwelder, H. S., & Wilson, W. A. (1991). GABAB-receptor-mediated inhibition of the N-methyl-D-aspartate component of synaptic transmission in the rat hippocampus. *The Journal of Neuroscience, 11*, 203–209.

Munoz, M. B., Padgett, C. L., Rifkin, R., Terunuma, M., Wickman, K., Contet, C., et al. (2016). A role for the GIRK3 subunit in methamphetamine-induced attenuation of GABAB receptor-activated GIRK currents in VTA dopamine neurons. *The Journal of Neuroscience, 36*, 3106–3114.

Munoz, M. B., & Slesinger, P. A. (2014). Sorting nexin 27 regulation of G protein-gated inwardly rectifying K^+ channels attenuates in vivo cocaine response. *Neuron, 82*, 659–669.

Mutneja, M., Berton, F., Suen, K.-F., Lüscher, C., & Slesinger, P. A. (2005). Endogenous RGS proteins enhance acute desensitization of GABA(B) receptor-activated GIRK currents in HEK-293T cells. *Pflügers Archiv / European Journal of Physiology, 450*, 61–73.

Nedergaard, S., Flatman, J. A., & Engberg, I. (1993). Nifedipine- and omega-conotoxin-sensitive Ca^{2+} conductances in guinea-pig substantia nigra pars compacta neurones. *The Journal of Physiology, 466*, 727–747.

Nestler, E. J., Terwilliger, R. Z., Walker, J. R., Sevarino, K. A., & Duman, R. S. (1990). Chronic cocaine treatment decreases levels of the G protein subunits Gi alpha and Go alpha in discrete regions of rat brain. *Journal of Neurochemistry, 55*, 1079–1082.

Neuhoff, H., Neu, A., Liss, B., & Roeper, J. (2002). I(h) channels contribute to the different functional properties of identified dopaminergic subpopulations in the midbrain. *The Journal of Neuroscience, 22*, 1290–1302.

Nicholson, K. L., & Balster, R. L. (2001). GHB: A new and novel drug of abuse. *Drug and Alcohol Dependence, 63*, 1–22.

Olpe, H. R., Koella, W. P., Wolf, P., & Haas, H. L. (1977). The action of baclofen on neurons of the substantia nigra and of the ventral tegmental area. *Brain Research, 134*, 577–580.

Otmakhova, N. A., & Lisman, J. E. (2004). Contribution of Ih and GABAB to synaptically induced afterhyperpolarizations in CA1: A brake on the NMDA response. *Journal of Neurophysiology, 92*, 2027–2039.

Padgett, C. L., Lalive, A. L., Tan, K. R., Terunuma, M., Munoz, M. B., Pangalos, M. N., et al. (2012). Methamphetamine-evoked depression of GABA(B) receptor signaling in GABA neurons of the VTA. *Neuron, 73*, 978–989.

Phillips, P. E., & Stamford, J. A. (2000). Differential recruitment of N-, P- and Q-type voltage-operated calcium channels in striatal dopamine release evoked by 'regular' and 'burst' firing. *Brain Research, 884*, 139–146.

Pitman, K. A., Puil, E., & Borgland, S. L. (2014). GABA(B) modulation of dopamine release in the nucleus accumbens core. *The European Journal of Neuroscience, 40*, 3472–3480.

Puopolo, M., Raviola, E., & Bean, B. P. (2007). Roles of subthreshold calcium current and sodium current in spontaneous firing of mouse midbrain dopamine neurons. *The Journal of Neuroscience, 27*, 645–656.

Rice, M. E., Cragg, S. J., & Greenfield, S. A. (1997). Characteristics of electrically evoked somatodendritic dopamine release in substantia nigra and ventral tegmental area in vitro. *Journal of Neurophysiology, 77*, 853–862.

Santiago, M., Machado, A., & Cano, J. (1993a). Regulation of the prefrontal cortical dopamine release by GABAA and GABAB receptor agonists and antagonists. *Brain Research, 630*, 28–31.

Santiago, M., Machado, A., & Cano, J. (1993b). In vivo release of dopamine from rat striatum, substantia nigra and prefrontal cortex: Differential modulation by baclofen. *British Journal of Pharmacology, 109*, 814–818.

Schmitz, Y., Schmauss, C., & Sulzer, D. (2002). Altered dopamine release and uptake kinetics in mice lacking D2 receptors. *The Journal of Neuroscience, 22*, 8002–8009.

Schultz, W. (1998). Predictive reward signal of dopamine neurons. *Journal of Neurophysiology, 80*, 1–27.

Schwenk, J., Metz, M., Zolles, G., Turecek, R., Fritzius, T., Bildl, W., et al. (2010). Native GABA(B) receptors are heteromultimers with a family of auxiliary subunits. *Nature, 465*, 231–235.

Schwenk, J., Pérez-Garci, E., Schneider, A., Kollewe, A., Gauthier-Kemper, A., Fritzius, T., et al. (2016). Modular composition and dynamics of native GABAB receptors identified by high-resolution proteomics. *Nature Neuroscience, 19*, 233–242.

Sharpe, A. L., Varela, E., Bettinger, L., & Beckstead, M. J. (2015). Methamphetamine self-administration in mice decreases GIRK channel-mediated currents in midbrain dopamine neurons. *The International Journal of Neuropsychopharmacology, 18*.

Shoaib, M., Swanner, L. S., Beyer, C. E., Goldberg, S. R., & Schindler, C. W. (1998). The GABAB agonist baclofen modifies cocaine self-administration in rats. *Behavioural Pharmacology, 9*, 195–206.

Sugita, S., Johnson, S. W., & North, R. A. (1992). Synaptic inputs to GABAA and GABAB receptors originate from discrete afferent neurons. *Neuroscience Letters, 134*, 207–211.

Tan, K. R., Yvon, C., Turiault, M., Mirzabekov, J. J., Doehner, J., Labouèbe, G., et al. (2012). GABA neurons of the VTA drive conditioned place aversion. *Neuron, 73*, 1173–1183.

Terrier, J., Ort, A., Yvon, C., Saj, A., Vuilleumier, P., & Lüscher, C. (2011). Bi-directional effect of increasing doses of baclofen on reinforcement learning. *Frontiers in Behavioral Neuroscience, 5*, 40.

Terunuma, M., Vargas, K. J., Wilkins, M. E., Ramírez, O. A., Jaureguiberry-Bravo, M., Pangalos, M. N., et al. (2010). Prolonged activation of NMDA receptors promotes dephosphorylation and

alters postendocytic sorting of GABAB receptors. *Proceedings of the National Academy of Sciences of the United States of America, 107*, 13918–13923.

Tritsch, N. X., Ding, J. B., & Sabatini, B. L. (2012). Dopaminergic neurons inhibit striatal output through non-canonical release of GABA. *Nature, 490*, 262–266.

Tsai, H.-C., Zhang, F., Adamantidis, A., Stuber, G. D., Bonci, A., De Lecea, L., et al. (2009). Phasic firing in dopaminergic neurons is sufficient for behavioral conditioning. *Science (New York, NY), 324*, 1080–1084.

Turecek, R., Schwenk, J., Fritzius, T., Ivankova, K., Zolles, G., Adelfinger, L., et al. (2014). Auxiliary GABAB receptor subunits uncouple G protein βγ subunits from effector channels to induce desensitization. *Neuron, 82*, 1032–1044.

van Zessen, R., Phillips, J. L., Budygin, E. A., & Stuber, G. D. (2012). Activation of VTA GABA neurons disrupts reward consumption. *Neuron, 73*, 1184–1194.

Vigot, R., Barbieri, S., Bräuner-Osborne, H., Turecek, R., Shigemoto, R., Zhang, Y. P., et al. (2006). Differential compartmentalization and distinct functions of GABAB receptor variants. *Neuron, 50*, 589–601.

Wang, H.-L., Qi, J., Zhang, S., Wang, H., & Morales, M. (2015). Rewarding effects of optical stimulation of ventral tegmental area glutamatergic neurons. *The Journal of Neuroscience, 35*, 15948–15954.

Watabe-Uchida, M., Zhu, L., Ogawa, S. K., Vamanrao, A., & Uchida, N. (2012). Whole-brain mapping of direct inputs to midbrain dopamine neurons. *Neuron, 74*, 858–873.

Westerink, B. H., de Boer, P., Santiago, M., & De Vries, J. B. (1994). Do nerve terminals and cell bodies of nigrostriatal dopaminergic neurons of the rat contain similar receptors? *Neuroscience Letters, 167*, 109–112.

Westerink, B. H., Santiago, M., & De Vries, J. B. (1992). The release of dopamine from nerve terminals and dendrites of nigrostriatal neurons induced by excitatory amino acids in the conscious rat. *Naunyn-Schmiedeberg's Archives of Pharmacology, 345*, 523–529.

White, F. J. (1996). Synaptic regulation of mesocorticolimbic dopamine neurons. *Annual Review of Neuroscience, 19*, 405–436.

White, J. H., Wise, A., Main, M. J., Green, A., Fraser, N. J., Disney, G. H., et al. (1998). Heterodimerization is required for the formation of a functional GABA(B) receptor. *Nature, 396*, 679–682.

Wickman, K., Karschin, C., Karschin, A., Picciotto, M. R., & Clapham, D. E. (2000). Brain localization and behavioral impact of the G-protein-gated K+ channel subunit GIRK4. *The Journal of Neuroscience, 20*, 5608–5615.

Xi, Z.-X., Ramamoorthy, S., Shen, H., Lake, R., Samuvel, D. J., & Kalivas, P. W. (2003). GABA transmission in the nucleus accumbens is altered after withdrawal from repeated cocaine. *The Journal of Neuroscience, 23*, 3498–3505.

Xi, Z. X., & Stein, E. A. (1998). Nucleus accumbens dopamine release modulation by mesolimbic GABAA receptors-an in vivo electrochemical study. *Brain Research, 798*, 156–165.

Xi, Z. X., & Stein, E. A. (2000). Increased mesolimbic GABA concentration blocks heroin self-administration in the rat. *The Journal of Pharmacology and Experimental Therapeutics, 294*, 613–619.

Xia, Y., Driscoll, J. R., Wilbrecht, L., Margolis, E. B., Fields, H. L., & Hjelmstad, G. O. (2011). Nucleus accumbens medium spiny neurons target non-dopaminergic neurons in the ventral tegmental area. *The Journal of Neuroscience, 31*, 7811–7816.

Zhang, K., Tarazi, F. I., Campbell, A., & Baldessarini, R. J. (2000). GABA(B) receptors: Altered coupling to G-proteins in rats sensitized to amphetamine. *Neuroscience, 101*, 5–10.

Zweifel, L. S., Parker, J. G., Lobb, C. J., Rainwater, A., Wall, V. Z., Fadok, J. P., et al. (2009). Disruption of NMDAR-dependent burst firing by dopamine neurons provides selective assessment of phasic dopamine-dependent behavior. *Proceedings of the National Academy of Sciences of the United States of America, 106*, 7281–7288.