Distinct roles of synaptic and extrasynaptic GABA<sub>A</sub> receptors in striatal inhibition dynamics

Ruixi Luo, John G. Partridge and Stefano Vicini*

Department of Pharmacology and Physiology, Georgetown University School of Medicine, Washington, DC, USA

INTRODUCTION

Striatonigral and striatopallidal projecting medium spiny neurons (MSNs) express dopamine D1 (D1<sup>+</sup>) and D2 receptors (D2<sup>+</sup>) respectively. Both classes receive extensive GABAergic input via expression of synaptic, perisynaptic, and extrasynaptic GABA<sub>A</sub> receptors. The activation patterns of different presynaptic GABAergic neurons produce transient and sustained GABA<sub>A</sub> receptor mediated conductance that fulfill distinct physiological roles. We performed single and dual whole cell recordings from striatal neurons in mice expressing fluorescent proteins in interneurons and MSNs. We report specific inhibitory dynamics produced by distinct activation patterns of presynaptic GABAergic neurons as source of synaptic, perisynaptic, and extrasynaptic inhibition. Synaptic GABA<sub>A</sub> receptors in MSNs contain the α<sub>2</sub>, α<sub>2</sub>, and α<sub>δ</sub> subunit. In addition, there is evidence for the developmental increase of the α<sub>1</sub> subunit that contributes to faster inhibitory post-synaptic current (IPSC). Tonic GABAergic currents in MSNs from adult mice are carried by extrasynaptic receptors containing the α<sub>4</sub> and δ subunit, while in younger mice this current is mediated by receptors that contain the α<sub>5</sub> subunit. Both forms of tonic currents are differentially expressed in D1<sup>+</sup> and D2<sup>+</sup> MSNs. This study extends these findings by relating presynaptic activation with pharmacological analysis of inhibitory conductance in mice where the β3 subunit is conditionally removed in fluorescently labeled D2<sup>+</sup> MSNs. This suggests that the β3 subunit is not a component of the adult extrasynaptic receptor pool, in contrast to what has been shown for tonic current in young mice. Deletion of the β3 subunit from D2<sup>+</sup> MSNs however, removed slow spontaneous IPSCs, implicating its role in mediating synaptic input from striatal neurogliaform interneurons.

Keywords: GABA, tonic inhibition, striatum, patch-clamp, Cre-lox genetics

MATERIALS AND METHODS

The use of several strains of transgenic mice examined in this study to genetically identify rare striatal interneurons and have...
been described previously (Luo et al., 2013). These include the BAC-xyg-eGFP and parv-Cre; rosa26-tdTom. Conditional and neuron-specific GABAαβ3 subunit knockout (KO) mice and appropriate control mice were produced as reported in Janssen et al., 2011, by crossing floxed β3 mice (B3F1) (Jackson Labs # 008330; Ferguson et al., 2007) to transgenic mice that express Cre recombinase under the ddx2 promoter (GENSKY, ER44; Gong et al., 2007). These Cre-dependent β3 subunit KO mice were subsequently crossed to “floxed-stop” rosa26-tdTom mice (Jackson Labs # 007914; Madisen et al., 2011); a second Cre-dependent line to allow visual identification of neurons lacking the β3 receptor subunit restricted to D2+ neurons. We designate this line as ddx2-CreB6F1/+, Rosa26ΔloxP. Control mice used in these studies included ddx2-CreB6F1/+, Rosa26ΔloxP and Cre-negative β3F1/+, Rosa26ΔloxP. We did not detect any statistical differences between these two genotypes and combined them for control experiments. We employed commercially available genotyping of tail biopsies of littermates via Transnetyx, Inc. (Cordova, TN, USA) before conducting experiments. We also used global GABAαβ3- receptor subunit knockout mice previously described (Mihalek et al., 1999; Janssen et al., 2009).

**BRAIN SLICE PREPARATION**

Male and female mice (post-natal day 14–18) were sacrificed by decapitation in agreement with the guidelines of the AMVA Panel on Euthanasia and the Georgetown University ACCU. The whole brain was removed and placed in an ice-cold slicing solution (in mM): NaCl (124), KCl (4.5), Na2HPO4 (1.2), NaHCO3 (25), sucrose (75) (all from Sigma, St. Louis, MO, USA). Coronal slices (250 μm) containing striatum were prepared using a Vibratome 3000 Plus Slicing System (Vibratome, St. Louis, MO, USA) in slicing solution. Upon hemi-sectioning, tissue was maintained at pH 7.4 by continuous bubbling with 95% O2/5% CO2.

**WHOLE-CELL RECORDINGS**

Acute slices were visualized under an upright microscope (E600FN, Nikon) equipped with Nomarski optics and a 60× water immersion objective with a long working distance (2 mm) and high numerical aperture (1.0). Neurons were identified with epi-fluorescent excitation of the tissue with a mercury-based lamp and standard filter sets. Recording pipettes, 4–6 MΩ in resistance, were prepared from borosilicate glass capillaries (Witterroll II; Drummond) and filled with potassium chloride (KCl) or potassium gluconate (Kgluc)-based (for interneurons) internal solutions. The KCl-based internal solution contained (in mM): NaCl (85), KCl (2.5), CaCl2 (2.0), MgCl2 (1), and dextrose (10.0) at 305 mOsm and adjusted to pH 7.2 with KOH. This high chloride internal solution enhanced the detection of GABAergic events, placing their reversal potential near 0 mV. In Kgluc-based internal solutions, KCl was replaced with equimolar (145 mM) Kglucanate and pH was adjusted with KOH.

All recordings presented here were performed at room temperature, 22–24°C. Voltage-clamp recordings were achieved using the whole-cell configuration of the patch-clamp technique at a holding potential of −70 mV using the Multiclamp 700B amplifier (Molecular Device Co., Sunnyvale, CA, USA). Synaptically coupled interneurons were subjected to holding current values which hyperpolarized neurons to a resting membrane potential of −70 mV in current-clamp mode. Access resistance was monitored periodically during recordings and experiments with >20% change were discarded. Membrane potential measurements were not corrected for liquid junction potential errors.

Stock solutions of bicuculline methobromide (BMR), tetrodotoxin (TTX), 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridine-3-ol, (THIP, gaboxadol), and sodium-2,3-dihydro-6-nitro-7-sulfamoyl-benzo[f]quinoxaline (NBQX) (all from Abcam Biochemicals Cambridge, MA, USA) were prepared in water. Etomidate (Sigma) was dissolved in dimethyl sulfoxide at a 30 mM stock solution (the working solution of 0.5 μM etomidate corresponds to a final concentration of 0.002% DMSO). Stock solutions were diluted to the desired working concentration in aCSF and applied locally through a Y tube (Murase et al., 1989; Heers and Liddens, 2002).

Recordings were filtered at 2 kHz with a low-pass Bessel filter and digitized at 5–10 kHz using a personal computer equipped with Digidata 1322A data acquisition board and pCLAMP10 software (both from Molecular Devices). Data analysis, curve fitting, and Figure preparation were performed with Clampfit® software (Molecular Devices). Spontaneous or miniature inhibitory postsynaptic currents (sIPSCs and mIPSCs) were identified using a semi-automated threshold-based mini detection software (Mini Analysis, Synapsoft Inc., Fort Lee, NJ, USA) and were visually confirmed. IPSC averages were based on more than 50 non-overlapping events, and decay kinetics were determined with averaged IPSC traces using double exponential curve fittings and reported as weighted time constants (Tw).

$$T_w = t_e \times \left[ A_1/(A_1 + A_2) \right] + t_i \times \left[ A_2/(A_1 + A_2) \right]$$

where $t_e$ is the decay time constant for a particular component of the curve and $A_1$ is the peak amplitude of the corresponding component. Similarly, decay time constants of unitary evoked IPSCs in synaptically coupled pairs were determined from the average of N evoked responses. mIPSCs were isolated with TTX (0.5 μM) and NBQX (5 μM) while NBQX was not included in sIPSC measurements to not perturb the network activity after removing rapidly decaying sIPSCs as previously described (Forcelli et al., 2012).

THIP mediated inward currents were primarily measured with an all-points histogram that measured the mean holding current 10 s before and during drug application (Luo et al., 2013). Holding current changes during high frequency stimulation of synaptically connected pairs were assessed during depolarization of presynaptic neurons and low pass filtering of the post-synaptic current recording (2–5 Hz).
We then characterized the change in holding current ($\Delta I_{\text{hold}}$) of subunit-containing GABAA receptor superagonist (Brown et al., 2013). Single presynaptic action potentials produced reliable IPSCs when neurons were synaptically coupled (Figure 1A). The rise and decay time of evoked IPSCs from these two interneuron classes differed significantly (Figure 1B).

We then characterized the change in holding current ($\Delta I_{\text{hold}}$) in post-synaptic MSNs in response to increasing action potential frequency of presynaptic interneurons (Figure 1C). Figure 1D summarizes these data and illustrates the occurrence of tonic current in MSNs resulting from presynaptic activation.

Tonic GABAAergic currents in MSNs from adult mice are carried by extrasynaptic receptors containing the $\alpha$ and $\beta$ subunit (Santhakumar et al., 2010), while in younger mice this current is mediated by receptors that contain the $\alpha$ and $\delta$ subunit (Janssen et al., 2008; Janssen et al., 2009). These studies have shown that deletion of the $\beta$ subunit removes GABAergic tonic current from adult MSNs while deletion of the $\beta$ subunit is not a component of tonic current in young MSNs. Although $\alpha$ and $\delta$ subunit mediated tonic current has been found in younger MSNs, it does not differ between $D1^+$ and $D2^+$ subtypes (Janssen et al., 2009). It is the differential expression of the $\beta$ subunit that has been suggested to account for the observed difference in tonic current between $D1^+$ and $D2^+$ subtypes.

To investigate if deletion of the $\beta$ subunit also affects tonic currents mediated by $\alpha$ and $\beta$ subunit, we used THIP (gaboxadol), a $\beta$ subunit-containing GABAA receptor superagonist (Brown et al., 2002). As shown in examples in Figure 2A and the summary data in Figure 2B, response to low doses of gaboxadol (2 $\mu$M) are abolished in $\beta$ but not $\beta$ subunit knock out mice. This suggests that, in contrast to what was previously shown for tonic current in young mice (Janssen et al., 2009), the $\beta$ subunit is not a component of $\beta$ subunit-containing extrasynaptic receptor pool in adult mice (Santhakumar et al., 2010).

Removing the $\beta$ subunit of GABAergic receptors from MSNs reduced whole cell current mediated by the general anesthetic etomidate, a $\beta$ subunit preferring modulator (Janssen et al., 2011). Here we extend these results by investigating the action of this general anesthetic on sIPSCs recorded from fluorescently identified $D2^+$ MSNs where the $\beta$ subunit is conditionally deleted. We used a concentration of etomidate (0.5 $\mu$M) that does not produce a sustained tonic current (Figure 3A). As shown in the example traces in Figure 3A and the summary data in Figure 3B, etomidate (0.5 $\mu$M) doubled the decay time of sIPSCs in control $D2^+$ MSNs but not in $D2^+$ MSNs with the $\beta$ subunit removed. sIPSCs from MSNs in $\beta$ subunit $^{-/-}$ mice were also significantly prolonged by etomidate.

Our previous results revealed that mIPSCs in unidentifed MSNs from mice where the $\beta$ subunit was conditionally deleted in $D2^+$ MSNs were significantly faster than in control littermates (Janssen et al., 2010). We refined these results by recording from fluorescent $D2^+$ MSNs and non-fluorescence ($D2^-$) MSNs in newly developed mice where the $\beta$ subunit is conditionally deleted in $D2^+$ MSNs that also express red fluorescence (tdr2- Cre/+; $\beta^3$-rule/+). Individual mIPSCs recorded in voltage clamp from control and $\beta$ subunit KO MSNs (Figure 4A) are averaged and fitted with double exponential decay to show the
FIGURE 2 | The β3 subunit does not associate with the δ subunit in extrasynaptic GABAA receptors. (A) Example traces illustrating 2 μM THIP induced current in control MSNs and D2+ MSNs from β3f/f;RosatdTom mice and the lack of response in MSN from δ−/− mice. Summary of the data obtained is shown in (B) together with the summary of currents (ΔI/Ihold) elicited by 10 μM THIP compared between MSN from control and δ−/− mice. Note that at 10 μM THIP begins to activate non-δ-containing receptors. ∗p < 0.05 paired two-tailed Student’s t test control group or Wilcoxon matched pairs test. The average increase in ΔI/Ihold in δ−/− MSNs is less compared to control but the difference is not significant.

FIGURE 3 | GABAA receptor subunits affect response to etomidate. (A) Example traces at a slow time scale (left) illustrating the lack of effect of 0.5 μM etomidate on holding current in D2+ MSNs deriving from control and β3f/f;RosatdTom compared to unidentified MSNs from δ−/− mice. On the right are shown superimposed the average normalized sIPSCs with exponential fits and weighted decay time constant in the absence and the presence of etomidate. (B) Summary graph comparing the weighted decay time constant of average sIPSCs measured in MSNs from the three genotypes in the absence and the presence of 0.5 μM etomidate. ∗p < 0.05 paired two-tailed Student’s t test control group or Wilcoxon matched pairs test. The average increase in Tw in δ−/− MSNs is less compared to control but the difference is not significant.

difference in decay kinetics (Figure 4B). As seen in the summary results (Figure 4C), in D2+ MSNs with the β3 subunit removed, mIPSCs decay faster compared to MSNs in control mice and also D2− MSNs in KO mice. Hentschke et al. (2009) showed that deletion of the β3 subunit in hippocampal CA1 pyramidal neurons removes slow sIPSC. Therefore we speculate that another contributing factor to the change in average mIPSC kinetics in D2+ MSNs with deletion of the β3 subunit could be the lack of slow IPSCs mediated by presynaptic NGF-NPY interneurons, as shown in the examples in Figure 4D. To investigate this, we looked for the occurrence of slow sIPSCs in several D2+ MSNs in control and in mice with β3 subunit conditional deletion. Spontaneous slow IPSCs occurred very infrequently (< 1 event/5 min), in 12% (6/51) of D2+ MSNs from 10 control mice, 13% (4/31) of MSNs from 5 δ subunit−/− mice, but they were not observed in 58 D2+ MSNs from 13 mice with the β3 subunit deletion. The differences observed were statistically significant for D2+ MSNs in mice with β3 subunit conditional deletion compared to wild type or δ subunit−/− mice (P = 0.009 and 0.013; Fisher’s Exact Test). This is supported by pair recordings from putative NGF-NPY interneurons and D2+ MSNs with (Figure 4E left) and without the β3 subunit (Figure 4E right). The NFG-NPY cells were identified in叒

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A lack of slow synaptic responses were observed in four additional NGF-NPY interneuron and D2β3 subunit conditional deletion mice. To further investigate this we recorded action potentials in NGF-NPY neurons and large slow IPSCs in D2β3 subunit deletion mice by soma size and characteristic firing pattern (inset). As illustrated a burst of action potentials in a presynaptic NGF-NPY neuron elicited a large slow IPSC only in D2β3−/− MSNs. The NGF-NPY cells were identified in the control neuron (left) and not in the D2β3−/− MSNs. The β3 subunit deletion mice by soma size and characteristic firing pattern (inset).

**DISCUSSION**

Synaptic, perisynaptic, and extrasynaptic GABA<sub>A</sub> receptors have distinct roles in mediating key aspects of neuronal microcircuitry that have been extensively characterized in the cerebellum (Farbant and Iversen, 2003) and the thalamus (Ibañez-Sandoval et al., 2007). These roles include mediating fast feedforward and feedback inhibition, dendritic shunting, regulation of excitability (Semyanov et al., 2004), and generation of oscillatory activity (Cobb et al., 1995; Levesque et al., 2012). Striatal MSNs have crucial roles in controlling movement and are implicated in several neurological disorders (Graybiel et al., 1994). GABA is critical to striatal function as MSNs are GABAergic in nature, forming inhibitory collateral axons among themselves (Gittis and Kreitzer, 2012). Further, GABAergic interneurons make extensive synaptic connections within the entire nucleus. Yet the role of GABAergic inhibition in this crucial area is poorly understood. Our results extend recent important findings on the dynamics of GABAergic inhibition and GABA<sub>A</sub> receptors in striatal neurons.

The power of mouse genetics has allowed in recent years the ability to identify distinct subtypes of GABAergic interneurons by expressing fluorescent markers (Tepper et al., 2010; Gittis and Kreitzer, 2012). We recently reported that NGF-NPY interneurons and the FS-PV interneurons have high synaptic connectivity with MSNs and exhibit nicotinic acetylcholine receptor mediated responses (Luo et al., 2013). In the present study, we refined those results and quantified the differences in both rise and decay time of evoked IPSCs in MSNs for presynaptic NGF-NPY and FS-PV interneurons. In Luo et al. (2013), we have also shown that low frequency (<5 Hz) activation of NGF-NPY can produce sustained GABAergic currents in MSNs. This is different from FS-PV interneurons that require higher presynaptic firing rate. We confirmed and better quantified those results in the present study. However, we also show that higher presynaptic firing of NGF-NPY interneuron will produce massive GABAergic conductance. However, one should consider that our studies were performed at room temperature, which may differently regulate GABA transporter and thus synaptic and extrasynaptic GABA affecting the integration of IPSCs. The question that arises from these data is what GABA<sub>A</sub> receptors are activated by distinct presynaptic interneurons and the FS-PV interneurons have high synaptic connectivity with MSNs and exhibit nicotinic acetylcholine receptor mediated responses (Luo et al., 2013). In the present study, we refined those results and quantified the differences in both rise and decay time of evoked IPSCs in MSNs for presynaptic NGF-NPY and FS-PV interneurons. In Luo et al. (2013), we have also shown that low frequency (<5 Hz) activation of NGF-NPY can produce sustained GABAergic currents in MSNs. This is different from FS-PV interneurons that require higher presynaptic firing rate.

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the result that deletion of the β3 subunit but not the δ subunit affects the prolongation of synaptic decay by the general anesthetic etomidate.

Taken together these data allow us to partially model the subunit composition of synaptic and extrasynaptic GABAAR receptor in striatal MSNs, and propose that synaptic but not extrasynaptic GABAAR receptor must contain the β3 subunit. In contrast, the δ subunit is restricted to extrasynaptic GABAAR receptors as expected from current evidence in other brain areas. What is the role of β3 and δ subunits in perisynaptic receptors? Current models propose perisynaptic receptors as central mediators to the synaptic action of neuropeptide neurons in the hippocampus (Capogna and Pearce, 2011). Clearly more studies are needed to extend these findings to other brain regions. The data presented here, suggest that removal of the β3 subunit affects the synaptic action of neuropeptide neuron similarly in the striatum, by significantly reducing the occurrence of spontaneous slow IPSCs (Fishers’s Exact Test). The infrequent finding of MSNs with slow sIPSCs suggests that the faster decay of synaptic currents associated with β3 subunit deletion in MSNs is not related to diminished activity at NPY-NGF and MSN synapses, but rather to enhanced expression of α1 subunit-containing synaptic receptors as we previously proposed (Jansen et al., 2011). The data presented show that this effect is indeed specifically due to the deletion of the β3 subunit. In summary, this work emphasizes that in order to better understand GABAergic control of striatal microcircuitry, we need to consider the activation mode and heterogeneity of perisynaptic interneurons together with the presence of specific GABAAR receptor subtypes with distinct function.

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