

Gubbi Govindaiah, Tongfei Wang, Martha U. Gillette, Shane R. Crandall and Charles L. Cox

J Neurophysiol 104:2757-2765, 2010. First published Sep 8, 2010; doi:10.1152/jn.00361.2010

You might find this additional information useful...

This article cites 63 articles, 25 of which you can access free at:

<http://jn.physiology.org/cgi/content/full/104/5/2757#BIBL>

Updated information and services including high-resolution figures, can be found at:

<http://jn.physiology.org/cgi/content/full/104/5/2757>

Additional material and information about *Journal of Neurophysiology* can be found at:

<http://www.the-aps.org/publications/jn>

This information is current as of December 6, 2010 .

Regulation of Inhibitory Synapses by Presynaptic D₄ Dopamine Receptors in Thalamus

Gubbi Govindaiah,^{1,3} Tongfei Wang,³ Martha U. Gillette,^{3,4,5} Shane R. Crandall,⁵ and Charles L. Cox^{1,2,3,5}

¹Beckman Institute for Advanced Science and Technology, ²Departments of Pharmacology and ³Molecular and Integrative Physiology, ⁴Cell and Developmental Biology, and ⁵Neuroscience Program, University of Illinois, Urbana, Illinois

Submitted 19 April 2010; accepted in final form 3 September 2010

Govindaiah G, Wang T, Gillette MU, Crandall SR, Cox CL. Regulation of inhibitory synapses by presynaptic D₄ dopamine receptors in thalamus. *J Neurophysiol* 104: 2757–2765, 2010. First published September 8, 2010; doi:10.1152/jn.00361.2010. Dopamine (DA) receptors are the principal targets of drugs used in the treatment of schizophrenia. Among the five DA receptor subtypes, the D₄ subtype is of particular interest because of the relatively high affinity of the atypical neuroleptic clozapine for D₄ compared with D₂ receptors. GABA-containing neurons in the thalamic reticular nucleus (TRN) and globus pallidus (GP) express D₄ receptors. TRN neurons receive GABAergic afferents from globus pallidus (GP), substantia nigra pars reticulata (SNr), and basal forebrain as well as neighboring TRN neuron collaterals. In addition, TRN receives dopaminergic innervations from substantia nigra pars compacta (SNc); however, the role of D₄ receptors in neuronal signaling at inhibitory synapses is unknown. Using whole cell recordings from in vitro pallido-thalamic slices, we demonstrate that DA selectively suppresses GABA_A receptor-mediated inhibitory postsynaptic currents (IPSCs) evoked by GP stimulation. The D₂-like receptor (D_{2,3,4}) agonist, quinpirole, and selective D₄ receptor agonist, PD168077, mimicked the actions of DA. The suppressive actions of DA and its agonists were associated with alterations in paired pulse ratio and a decrease in the frequency of miniature IPSCs, suggesting a presynaptic site of action. GABA_A receptor agonist, muscimol, induced postsynaptic currents in TRN neurons were unaltered by DA or quinpirole, consistent with the presynaptic site of action. Finally, DA agonists did not alter intra-TRN inhibitory signaling. Our data demonstrate that the activation of presynaptic D₄ receptors regulates GABA release from GP efferents but not TRN collaterals. This novel and selective action of D₄ receptor activation on GP-mediated inhibition may provide insight to potential functional significance of atypical antipsychotic agents. These findings suggest a potential heightened TRN neuron activity in certain neurological conditions, such as schizophrenia and attention deficit hyperactive disorders.

INTRODUCTION

The thalamus relays sensory and motor information to the cerebral cortex and receives strong modulatory input back from the cortex. Both thalamocortical and corticothalamic projection neurons send collaterals to ventral thalamic nuclei (Jones 1975). GABA-containing thalamic reticular nucleus (TRN) neurons provide a major source of inhibitory synaptic input to thalamocortical (TC) neurons (Huguenard and McCormick 2007; Pinault 2004; Schofield et al. 2009). By modulating the flow of information through the thalamus, TRN has been hypothesized to play a major role in the control of attention and sensory processing (Guillery et al. 1998; Mayo 2009; McAl-

nan et al. 2008; Rees 2009; Yu et al. 2009). The TRN is also a key player in various types of rhythmic activity associated with certain arousal mechanisms and epileptiform activities (Hughes et al. 2002; Huguenard and McCormick 2007; Huntsman et al. 1999; McCormick and Bal 1997; Sohal et al. 2000; Steriade 1992, 1997; Steriade et al. 1993; vonKrosigk et al. 1993).

Dopamine (DA) is a major neuromodulator in the brain, and its dysfunction has been implicated in multiple human neurological and psychiatric disorders (Di Chiara 2002; Takahashi et al. 2006). Within thalamic circuitry, DA-dependent actions are thought to play a potentially significant role in emotion, attention, cognition, and complex somatosensory and visual processing (Takahashi et al. 2006). Alterations in thalamic DA receptors are also implicated in various neurological and psychiatric disorders (Behrendt 2006; Buchsbaum et al. 2006; Di Chiara 2002; Kane et al. 2009; Takahashi et al. 2006; Yasuno et al. 2004). Anatomical studies have shown that TRN receives a dopaminergic innervation from the substantia nigra pars compacta (SNc) (Anaya-Martinez et al. 2006; Gandia et al. 1993; Garcia-Cabezas et al. 2007, 2009; Sanchez-Gonzalez et al. 2005) and expresses DA receptors (Khan et al. 1998; Mrzljak et al. 1996). In addition, TRN receives GABAergic projections from globus pallidus (GP), substantia nigra pars reticulata (SNr), and basal forebrain (Anaya-Martinez et al. 2006; Asanuma and Porter 1990; Asanuma 1994; Bickford et al. 1994; Gandia et al. 1993; Hazrati and Parent 1991; Pare et al. 1990). Inhibitory innervations within TRN arise from local collaterals (Deleuze and Huguenard 2006; Lam et al. 2006; Shu and McCormick 2002). GABAergic terminals within TRN are hypothesized to express D₄ receptors (Ariano et al. 1997; Defagot et al. 1997; Mrzljak et al. 1996); however, the action of DA on GABAergic inhibitory signaling in TRN has not been explored. In this study, we found that DA, via presynaptic D₄ receptors, selectively suppresses GABA_A-receptor mediated inhibition arising from GP efferents without altering intra-TRN inhibitory signaling.

METHODS

The present study was performed on Sprague Dawley rats (postnatal age 11–20 days). All experimental procedures were carried out in accordance with the National Institute of Health Guidelines for the Care and Use of Laboratory Animals and approved by the University of Illinois Animal Care and Use committee. Animals were maintained with 12 h ON-OFF light/dark schedule in a temperature-controlled environment, and food and water were provided ad libitum.

Brain slices containing thalamus and GP were prepared as previously described with modifications (Lee et al. 2007). Rats were deeply

Address for reprint requests and other correspondence: G. Govindaiah, 2365 Beckman Institute for Advanced Science and Technology, 405 N. Matthew Ave., Urbana, IL 61801 (E-mail: goviks@life.uiuc.edu).

anesthetized with sodium pentobarbital (50 mg/kg) and decapitated. The brains were quickly removed and placed into chilled (4°C), oxygenated (5% CO₂-95% O₂) slicing medium containing (in mM) 2.5 KCl, 1.25 NaH₂PO₄, 10.0 MgCl₂, 2.0 CaCl₂, 26.0 NaHCO₃, 11.0 glucose, and 234.0 sucrose. Brain slices (250–300 μm thick) were cut in the horizontal plane using a vibrating tissue slicer (Leica, Germany). The slices were transferred to a holding chamber containing oxygenated, physiological solution and incubated (32°C) for ≥1 h prior to recording. The physiological solution contained (in mM) 126.0 NaCl, 2.5 KCl, 1.25 NaH₂PO₄, 2.0 MgCl₂, 2.0 CaCl₂, 26.0 NaHCO₃, and 10.0 glucose. The solution was continuously gassed with 95% O₂-5% CO₂ to a final pH of 7.4. Individual slices were transferred to a submersion type recording chamber maintained at 30 ± 1°C (mean ± SD) and continuously superfused (3 ml/min) with oxygenated solution.

Recording procedures

Whole cell recordings were obtained using a microscope equipped with differential interference contrast (DIC) optics (Axioskop 2FS, Carl Zeiss) similar to that previously used (Govindaiah and Cox 2006a,b). Specific thalamic nuclei were distinguished using a low-power objective, and a high-power water-immersion objective was used to identify individual neurons. Recording pipettes were pulled from borosilicate glass tubing and had tip resistances of 4–7 MΩ. For voltage clamp recordings, the pipette solution contained (in mM) 117.0 Cs-gluconate, 13.0 CsCl, 1.0 MgCl₂, 0.07 CaCl₂, 0.1 EGTA, 10.0 HEPES, 2.0 Na₂-ATP, and 0.4 Na-GTP. For current clamp experiments, the pipette solution contained (in mM) 117.0 K-gluconate, 13.0 KCl, 1.0 MgCl₂, 0.07 CaCl₂, 0.1 EGTA, 10.0 HEPES, 2.0 Na₂-ATP, 0.4 Na-GTP, and 0.3% biocytin. The pH and osmolarity of internal solution were adjusted to 7.3 and ~290 mosM, respectively. The internal solution resulted in a 10 mV junction potential that has been corrected in the voltage measures. After forming whole cell configuration, the recording was allowed to stabilize for ≥5 min prior to data acquisition. Inhibitory postsynaptic currents (IPSCs) were optimized by using the cesium (Cs⁺)-based internal solution and a 0 mV holding potential. All signals were obtained using a Multiclamp 700 amplifier (Molecular Devices, Foster City, CA). For current-clamp recordings, an active bridge circuit was continuously monitored and, if necessary, adjusted to balance the drop in potential produced by passing current through the recording electrode. Recordings included in this study had initial access resistances ranging from 5 to 12 MΩ and typically remained stable throughout the recording. Data were omitted from the analyses if initial access resistance changed by >20%. Only neurons that exhibited stable baseline with resting membrane potentials greater than -55 mV and overshooting action potentials were included for data analyses.

Stimulation procedures

IPSCs were evoked in TRN neurons by electrically stimulating GP (>0.5 mm lateral to TRN border, Fig. 1A) using monopolar electrode (200–700 μA, 50 μs duration). The stimulus intensity typically ranged from 200 to 400 μA, but on occasions, ≤700 μA was used if no response was observed at the lower intensities. The actions of the dopaminergic agonists were reversible, thereby suggesting a lack of damage to afferent fibers from the stimulus paradigm. IPSCs were pharmacologically isolated using *N*-methyl-D-aspartate (NMDA) and non-NMDA receptor antagonists, ±3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP, 10 μM) and 6,7-dinitroquinoxaline-2,3-dione (DNQX; 20 μM), respectively. In some neurons, focal application of glutamate via pressure ejection was used to evoke IPSCs in TRN neurons by neighboring neurons.

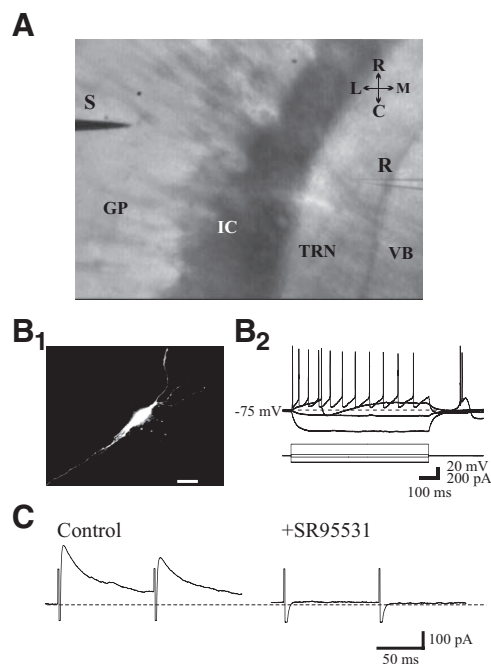


FIG. 1. *A*: image of horizontal brain slice at the level of globus pallidus (GP) and thalamic reticular nucleus (TRN) illustrating electrode placement. IC, internal capsule; VB, ventrobasal; R, recording pipette, S, stimulation electrode. *B1*: photomicrograph of a representative TRN neuron. The morphology of neuron was recovered by including a fluorescent dye Alexa-594 in recording pipette. *B2*: characteristic responses of a TRN neuron to hyper- and depolarizing current steps. TRN neurons display characteristic low-threshold calcium spikes (LTS) in response to hyperpolarizing current steps. *C*: paired pulse stimulation of GP evokes inhibitory postsynaptic currents (IPSCs) recorded in TRN neuron. The IPSCs were isolated by using *N*-methyl-D-aspartate (NMDA) receptor antagonist ±3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP, 10 μM) and non-NMDA receptor antagonist 6,7-dinitroquinoxaline-2,3-dione (DNQX, 20 μM) and were blocked by GABA_A receptor antagonist SR95531 (10 μM).

Drug administration

Concentrated stock solutions were originally prepared in appropriate solvents and diluted in physiological saline to final concentration just prior to use. Agonists were applied via a short bolus into an input line using a syringe pump (Govindaiah and Cox 2005). DA and SKF38393 were prepared fresh prior to application, and DA was prepared with 0.08% ascorbic acid to prevent oxidation. All antagonists were bath applied ≥5–10 min prior to subsequent agonist application. DA was purchased from Sigma (St. Louis, MO), whereas all remaining compounds were purchased from Tocris (Ellisville, MO).

Data acquisition and analyses

Quantification of evoked IPSC amplitude was performed on 5–10 consecutive responses in each experimental condition using pClamp software (Molecular Devices, Sunnyvale, CA). Miniature IPSCs (mIPSCs) were detected and analyzed using MiniAnalysis software (Synaptosoft, Leonia, NJ). The threshold for mIPSC detection was 10 pA and automatic detection was verified post hoc by visual analysis. The threshold for mIPSC detection was established from the baseline noise level recorded in the presence of GABA_A receptor antagonist (SR95531, 10 μM) and glutamate receptor antagonists, CPP and DNQX. For quantification of mIPSCs, the average mIPSC frequency was calculated from 60-s time windows: 1 min prior to agonist application and 30 s following agonist application (Govindaiah and Cox 2006b). To analyze glutamate evoked IPSCs in TRN, the frequency and amplitude of IPSCs were quantified from 1-s windows for

five consecutive sweeps for each condition. Due to lack of clear baseline in these cases, the events were manually detected and subsequently the frequency and amplitude of IPSCs quantified using MiniAnalysis software. Data are expressed as means \pm SD unless otherwise noted. Most analyses consisted of Student's *t*-test, paired test if appropriate, unless otherwise noted. *P* values <0.05 were considered statistically significant.

Histology

To confirm that the recordings were obtained from TRN neurons, the morphology of recorded TRN neurons was recovered by filling neurons with a fluorescent dye (Alexa-594, 50 μ M). Alexa-594 was included in the recording pipette and after recording, a z-stack of images was captured using custom-made two-photon laser scanning microscopy (Prairie Technologies, Middleton, WI) and collapsed using ImageJ software (National Institutes of Health).

RESULTS

The results presented in the present study were obtained from 80 TRN neurons. IPSCs in TRN neurons were evoked by GP stimulation (Fig. 1A) in the presence of NMDA and AMPA receptor glutamatergic antagonists, CPP (10 μ M) and DNQX (20 μ M), respectively. The eIPSCs were completely attenuated by the antagonist SR95531 (10 μ M), indicating that these events are mediated by GABA_A receptors (Fig. 1C).

DA suppresses GABA_A receptor-mediated inhibition in TRN neurons

We initially tested the effects of DA on GABA_A receptor-mediated IPSCs evoked by GP stimulation. Short-duration DA application (2.5–25 μ M, 20–30 s) reversibly suppressed the eIPSCs amplitudes in a reversible manner (Fig. 2A₁). Overall DA produced a concentration-dependent suppression of the eIPSC amplitude $\leq 43 \pm 11\%$ with an IC₅₀ of 5.1 μ M (Boltzman fit). As illustrated in Fig. 2A₂, DA reduced the eIPSC amplitude by $9 \pm 4\%$ (control: 496 \pm 143 pA, DA: 455 \pm 144 pA, *n* = 5, *P* < 0.001), $37 \pm 14\%$ (control: 481 \pm 128 pA, DA: 306 \pm 108 pA, *n* = 7, *P* < 0.0007), and $43 \pm 11\%$ (control: 469 \pm 124 pA, DA: 275 \pm 100 pA, *n* = 8, *P* < 0.0004) at 2.5, 10, and 25 μ M, respectively. There was no significant differences between 10 and 25 μ M DA.

Suppressive actions of DA are mediated via activation of D₄ receptors

We next used selective receptor agonists and antagonists to determine the receptor subtype(s) mediating the DA effect. Similar to DA, the D₂-like receptor (D_{2,3,4}) agonist quinpirole (5–10 μ M) and selective D₄ receptor agonist PD168077 (25–50 μ M) reversibly suppressed eIPSCs in TRN neurons (Fig. 2B). The suppressive action of quinpirole (10 μ M) was

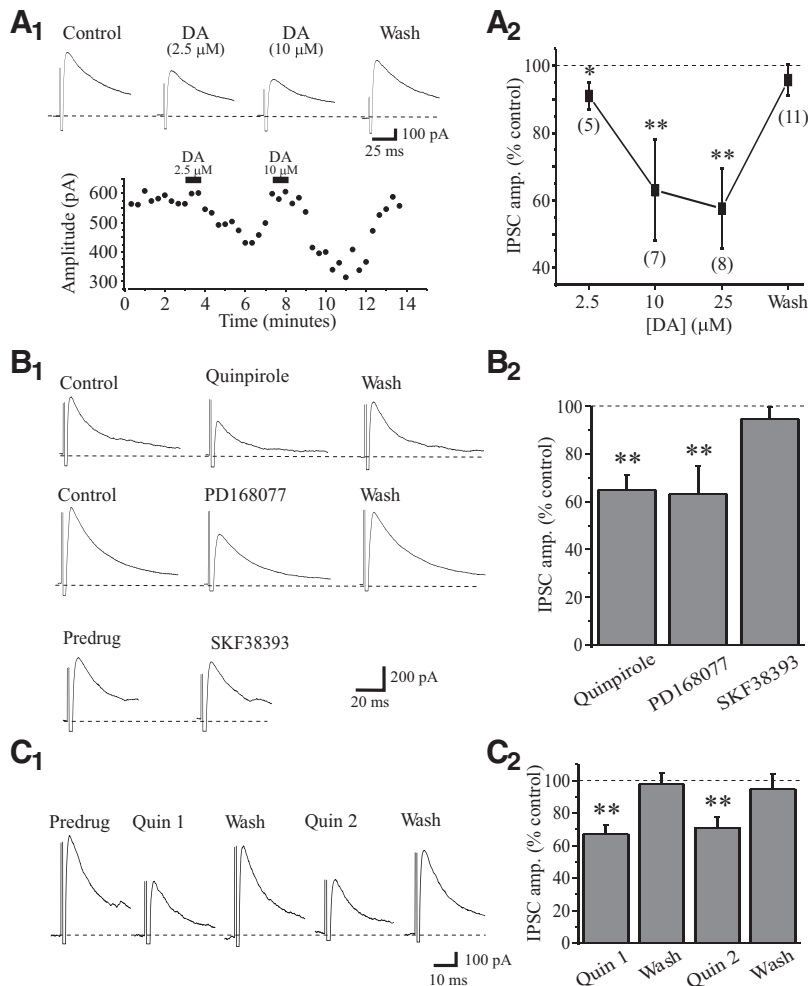


FIG. 2. Dopamine (DA) suppresses IPSCs in TRN neurons. A₁: in a representative neuron, the IPSC is reversibly attenuated by short application of DA at different concentrations (2.5 and 10 μ M) Top traces: representative IPSCs; bottom traces: the time course of DA-mediated actions. A₂: population data indicating a significant concentration-dependent suppression of evoked IPSC (eIPSC) by DA. **P* < 0.001, ***P* < 0.0001. The number of cells tested for each group is shown in parenthesis. B: D₂-like receptor agonist quinpirole and D₄ receptor agonist PD168077 mimic the actions of DA. B₁: in a representative TRN neuron, quinpirole (10 μ M) reversibly suppresses IPSC amplitude. In a different neuron, PD168077 (25 μ M) also reversibly suppresses IPSC amplitude by quinpirole (*n* = 10) and PD168077 (*n* = 5). ***P* < 0.0001.

reproducible to similar degree when applied at the interval of 5–10 min between each application (Fig. 2C). Short bath application (45 s) of quinpirole significantly reduced the eIPSC amplitude from 544 ± 245 to 347 ± 140 pA ($35.1 \pm 6.5\%$, $n = 10$, $P < 0.0001$, Fig. 2B). The magnitude of the quinpirole effects did not significantly differ from the DA-mediated effects ($P > 0.2$). The selective D_4 receptor agonist PD168077 ($25\text{--}50 \mu\text{M}$) also suppressed the eIPSC by $37 \pm 12\%$ (control: 565 ± 179 pA, PD168077: 355 ± 122 pA, $n = 5$, $P < 0.0001$, Fig. 2B2). In contrast, the D_1 -like receptor agonist SKF38393 ($10 \mu\text{M}$) did not alter eIPSC amplitude in all cells tested ($3.4 \pm 5\%$, control: 506 ± 182 pA, SKF38393: 501 ± 174 pA, $n = 4$, $P < 0.2$, Fig. 2B). We further confirmed the suppressive effects of D_2 -like and selective D_4 receptor agonists on eIPSCs using selective antagonists. As illustrated in Fig. 3A, quinpirole produced a significant reduction in the eIPSC amplitude from 366 ± 66 to 233 ± 33 pA ($36.3 \pm 5\%$, $n = 5$, $P < 0.002$), which recovered following washout (360 ± 70 pA). In the presence of D_2 -like receptor antagonist sulpiride ($10 \mu\text{M}$), subsequent quinpirole application significantly reduced eIPSC amplitude by $28.3 \pm 8.8\%$ (Fig. 3A, $n = 5$, $P < 0.02$). The quinpirole-mediated suppression of the eIPSC amplitude did

not significantly differ between control and sulpiride conditions (Fig. 3A, $P = 0.2$). Considering the repeated quinpirole applications in this experiment, in a different population of TRN cells, we made repeated quinpirole applications ($10 \mu\text{M}$, 10 min interval) in control conditions and found that the eIPSC amplitude was suppressed to a similar degree with each quinpirole application, suggesting no desensitization with repeated applications ($n = 4$, $P = 0.27$, Fig. 2C). Of the D_2 -like receptors (D_2 , D_3 , D_4), sulpiride has a higher affinity for D_2 and D_3 receptors (Werner et al. 1996), suggesting the suppression may be mediated via D_4 receptor activation.

To confirm the selective D_4 receptor activation by agonist PD168077, we next tested the actions of PD168077 in the presence of selective D_4 receptor antagonist L745870 (Patel et al. 1997). PD168077 ($25 \mu\text{M}$) reduced the eIPSC amplitude by $39.0 \pm 13.1\%$ in control conditions (Fig. 3B, control: 563 ± 207 pA, PD168077: 341 ± 137 pA, $n = 4$, $P < 0.001$). In the presence of L745870 ($50 \mu\text{M}$), the subsequent application of PD168077 did not alter the eIPSC amplitude (Fig. 3B, L745870: 485 ± 260 pA, PD168077 + L745870: 493 ± 254 pA, $n = 4$, $P = 0.1$). We further examined the sensitivity of the DA-mediated suppression of eIPSCs to the D_4 receptor

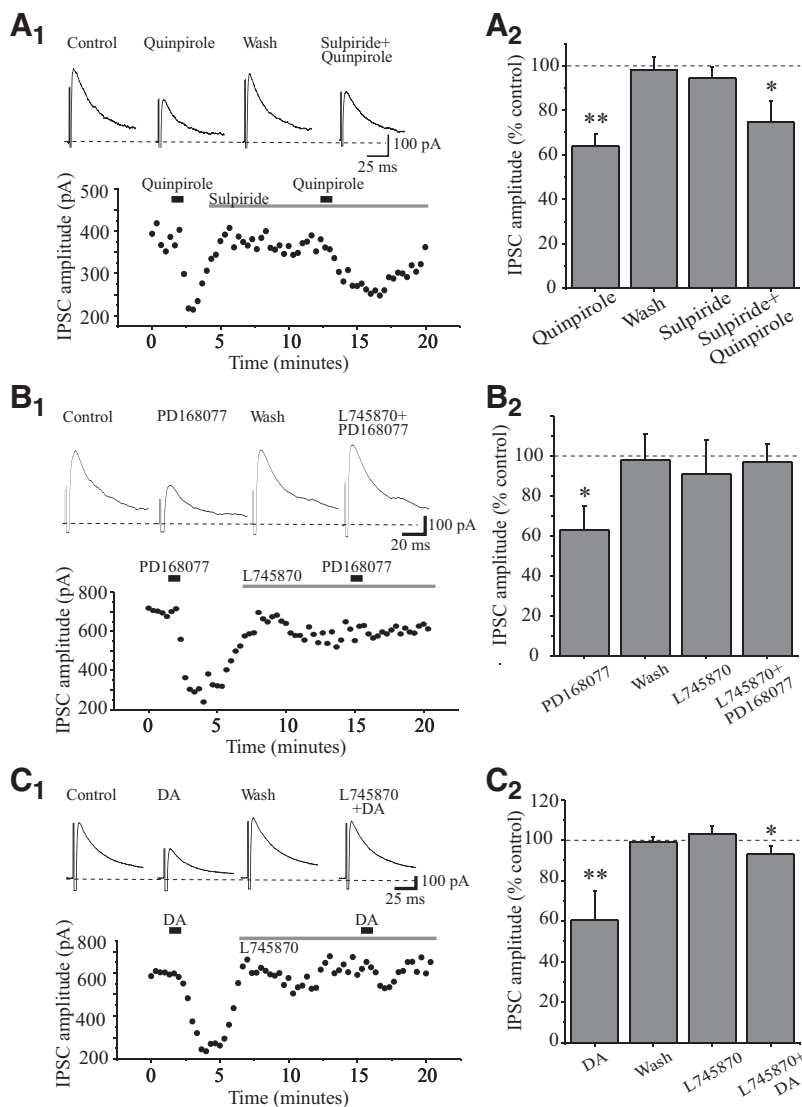


FIG. 3. Suppressive actions of DA on IPSCs mediated via D_4 receptor activation. *A1*: representative synaptic responses (top) and time course (bottom) illustrating that quinpirole ($10 \mu\text{M}$) suppresses the IPSC in a reversible manner. Following washout, the D_2 -like receptor antagonist sulpiride ($10 \mu\text{M}$) was bath applied, and the subsequent application of quinpirole still significantly attenuates IPSC amplitude. *A2*: population data illustrating the suppressive actions of quinpirole ($**P < 0.002$, $n = 5$), and this effect is not completely antagonized by sulpiride ($*P < 0.02$, $n = 5$). *B1*: in a different TRN neuron, PD168077 ($25 \mu\text{M}$) reversibly suppresses the IPSC similar to quinpirole. Following recovery, the selective D_4 receptor antagonist L745870 ($50 \mu\text{M}$) was bath applied, and the subsequent application of PD168077 does not alter IPSC amplitude. *B2*: population data illustrating reversible suppressive actions of PD168077 ($*P < 0.001$, $n = 4$). In the presence of L745870, PD168077 no longer alters the IPSC ($P = 0.1$, $n = 4$). *C1*: L745870 also blocks the DA-mediated suppression of the IPSC. In different TRN neurons, DA strongly attenuates the IPSC. In the presence of L745870 ($50 \mu\text{M}$), the DA-mediated suppression is greatly reduced. *C2*: population data illustrating the suppressive actions of DA alone ($**P < 0.007$, $n = 5$) and its reduced action in presence of L745870 ($*P < 0.03$, $n = 5$).

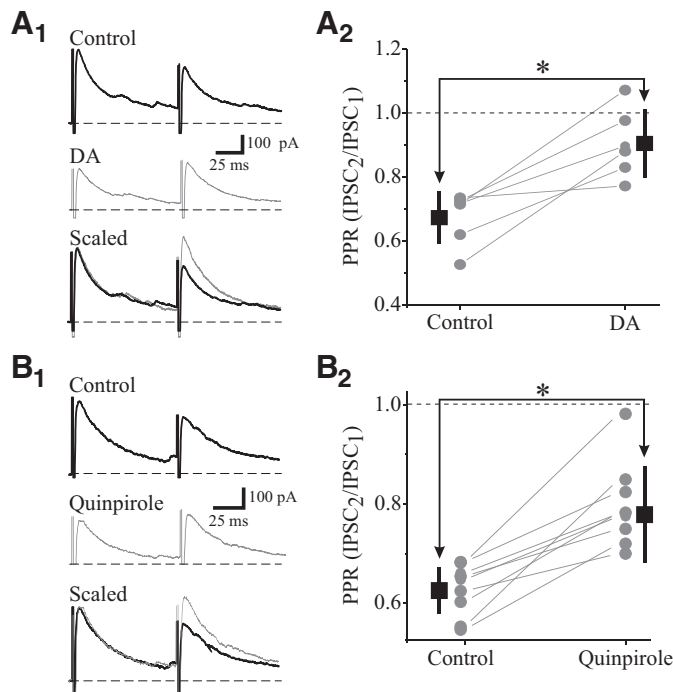


FIG. 4. DA reduces paired pulse depression of IPSC in TRN neurons. *A1*: representative IPSCs recorded from TRN neuron using paired-pulse stimulation [100 ms interspike interval (ISI)] of GP. DA (25 μ M) reduces the amplitude of the 1st IPSC (IPSC₁) with little alteration in the 2nd IPSC (IPSC₂), leading to an increase in paired pulse ratio (PPR). Scaling of the 1st IPSC clearly illustrates the reduction in paired pulse depression. *A2*: population data illustrate a significant increase in PPR by DA (* $P < 0.002$, $n = 6$), indicating a reduction in paired pulse depression. *B1*: in a different neuron, quinpirole (10 μ M) produces a similar alteration in PPR as DA. *B2*: population data illustrate a significant increase in PPR by quinpirole (* $P < 0.002$, $n = 8$).

antagonist. In these neurons, DA (10 μ M) significantly suppressed the eIPSC amplitude (Fig. 3C, control: 522 \pm 127 pA, DA: 314 \pm 191 pA, $n = 5$, $P < 0.007$). Following recovery, the D₄ receptor antagonist L745870 (25 μ M) was bath applied for 7–10 min. In the presence of L745870, the subsequent DA application did not alter the eIPSC amplitude significantly (Fig. 3C, control: 519 \pm 126 pA, L745870 + DA: 483 \pm 120 pA, $n = 5$, $P < 0.03$). Overall, these data indicate that activation of D₄ receptors attenuates evoked inhibitory synaptic transmission arising from GP stimulation.

Presynaptic D₄ receptors modulates GABAergic signaling in TRN

To examine whether the inhibitory actions of DA on IPSCs is mediated by a pre- or postsynaptic action, we studied the effect of DA and quinpirole on eIPSCs produced by paired pulse stimulation as well as their effect on miniature IPSCs (mIPSCs). Paired pulse stimulation within GP (75–125 ms interstimulus intervals, ISI) resulted in paired pulse depression of the eIPSCs in TRN neurons (Fig. 4). The paired pulse ratio (PPR: IPSC₂/IPSC₁) was calculated prior to and after agonist application. DA (25 μ M) attenuated the eIPSC and the PPR was significantly increased from 0.67 \pm 0.08 to 0.91 \pm 0.10 (Fig. 4A2; $n = 6$, $P < 0.002$), indicating a decrease in paired pulse depression. Similar to DA, quinpirole (10 μ M) also significantly increased the PPR from 0.63 \pm 0.04 to 0.79 \pm 0.09 (Fig. 4B; $n = 8$, $P < 0.002$). The alteration in PPR is

consistent with a presynaptic site of action such as a change in release properties (Zucker and Regehr 2002).

We next tested the effects of DA and dopaminergic agonists on mIPSC activity in TRN neurons. The mIPSCs were pharmacologically isolated using 1 μ M TTX, 10 μ M CPP, and 10 μ M DNQX, and recorded using a holding potential of 0 mV. Under these conditions, quinpirole (10 μ M, $n = 9$) and DA (25 μ M, $n = 3$) reduced mIPSC frequency but not mIPSC amplitude. Cumulative probability analyses indicate that quinpirole significantly increased the interevent interval (Fig. 5, B and C without significant alterations in mIPSC amplitude (*D* and *E*). Overall quinpirole decreased the frequency of mIPSCs by 37.0 \pm 12.5% (control: 1.0 \pm 0.4 Hz, quinpirole: 0.6 \pm 0.2 Hz, $n = 9$, $P < 0.001$, Fig. 5C). In contrast, quinpirole did not significantly alter mIPSC amplitude (control: 15.6 \pm 1.0 pA; quinpirole: 14.7 \pm 3.2 pA, $n = 9$; $P = 0.5$, Fig. 5E). The selective alteration in mIPSC frequency, but not mIPSC amplitude, is consistent with a presynaptic site of action.

Previous studies have demonstrated that activation of D₂-like receptors inhibits Ca²⁺ currents through a pertussis toxin

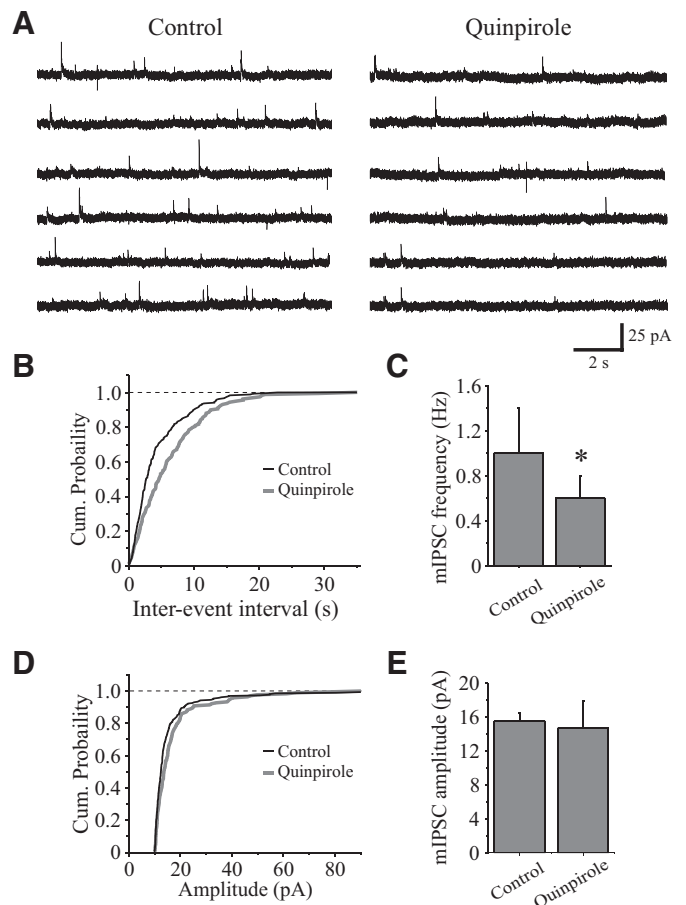


FIG. 5. Activation of D₂ receptors increases miniature IPSC (mIPSC) frequency but not mIPSC amplitude in TRN neurons. mIPSCs were recorded in presence of TTX (1 μ M). *A*: representative current traces reveal mIPSCs in control and following quinpirole (10 μ M) application. *B*: cumulative probability plots for neuron in *A* illustrating the increase in interevent intervals by quinpirole. *C*: population data revealing that quinpirole significantly reduces mIPSC frequency (* $P < 0.001$, $n = 9$). *D*: cumulative probability plot for neuron in *A* illustrating that mIPSC amplitude is unaltered by quinpirole. *E*: population data reveal quinpirole does not alter mIPSC amplitude ($P = 0.5$, $n = 9$).

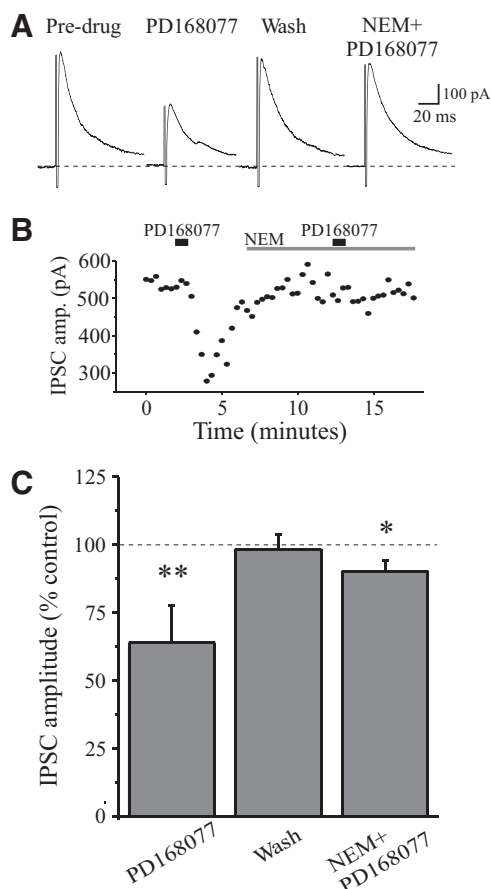


FIG. 6. The D_4 -mediated suppression of inhibition in TRN involves pre-synaptic inhibitory G proteins (G_i). *A*: in a representative TRN neuron, eIPSCs are reversibly attenuated by PD168077 ($25 \mu\text{M}$); however, the suppressive action of PD168077 is blocked in the presence of G_i -protein inhibitor *N*-ethylmaleimide (NEM) ($50 \mu\text{M}$). *B*: time course of the experiment illustrated in *A*. *C*: population data summarizing the effects of PD with and without NEM. $n = 5$, $*P < 0.01$, $**P < 0.02$.

(PTX)-sensitive G protein ($G_{i/o}$) (Yan et al. 1997). To determine whether the presynaptic D_4 receptor-mediated effect involves this G protein subtype, we examined the effect of the sulfhydryl alkylating agent *N*-ethylmaleimide (NEM), which disrupts coupling of PTX-sensitive $G_{i/o}$ type G proteins to Ca^{2+} channels (Shapiro et al. 1994). The suppressive action of D_4 receptor agonist PD168077 on eIPSC was blocked by NEM (Fig. 6). In control conditions, PD168077 ($25 \mu\text{M}$) reduced the eIPSC amplitude by $36.2 \pm 13.7\%$ ($n = 5$, $P < 0.01$). Bath application of NEM ($50 \mu\text{M}$) alone had no effect on the evoked IPSCs. In the presence of NEM, PD168077 produced a smaller suppression of the eIPSC ($9.9 \pm 4.1\%$); this is significantly smaller than that in the absence of NEM ($P < 0.02$), indicating that NEM-sensitive G_i proteins are coupled to presynaptic D_4 receptors.

As a measure of postsynaptic sensitivity, we tested if the DA and its agonists could alter GABA_A receptor-mediated currents in TRN neurons. GABA_A receptor-mediated currents were evoked by brief, focal application of the GABA_A receptor agonist muscimol at 20-s intervals. Muscimol ($50 \mu\text{M}$, 0.5 s duration) elicited repeatable outward currents (Fig. 7A) that were completely attenuated by SR95531 ($10 \mu\text{M}$, not shown). The muscimol-induced currents were unaltered by $25 \mu\text{M}$ DA

(Fig. 7B, control: $691 \pm 167 \text{ pA}$, DA: 667 ± 170 , $n = 3$; $P = 0.2$), or $10 \mu\text{M}$ quinpirole (Fig. 7B, control: 766 ± 222 , quinpirole: 729 ± 227 , $n = 6$; $P < 0.05$). These data suggest that DA does not regulate postsynaptic GABA_A receptors in TRN neurons. Overall these data indicate that the dopamine-mediated suppression of eIPSCs is due to a presynaptic action, thereby reducing GABA release from their terminals originating from GP.

DA-mediated suppression of inhibition is restricted to GP-TRN pathway

Our results clearly demonstrate that the activation of DA D_4 receptors suppress inhibitory synaptic transmission resulting from electrical stimulation of presumed GP efferents, but it is unclear if this is a general action affecting all inhibitory inputs onto TRN neurons. We next tested if DA could modulate intra-TRN inhibition considering these neurons form chemical synapses with each other (Deleuze and Huguenard 2006; Lam et al. 2006; Shu and McCormick 2002). To evoke intra-TRN inhibitory responses, we focally applied glutamate via pressure ejection within TRN near our recording. As shown in Fig. 8A, glutamate ($500 \mu\text{M}$, 50 ms) produced an inward current (likely via direct depolarization and/or electrical coupling) along with an increase in spontaneous IPSCs (sIPSCs). These sIPSCs were completely antagonized by a GABA_A receptor antagonist SR95531 (Fig. 8A, SR95531). The glutamate-evoked IPSCs had an average frequency of $23.7 \pm 11.4 \text{ Hz}$ (Fig. 8B, $n = 6$). After obtaining a consistent IPSCs resulting from glutamate application, quinpirole ($10 \mu\text{M}$, 45–60 s) was applied via bolus. Quinpirole did not alter the frequency of glutamate-evoked sIPSCs (Fig. 8B, control: $25.8 \pm 11.3 \text{ Hz}$, quinpirole: $24.3 \pm 10.9 \text{ Hz}$, $n = 5$, $P = 0.3$). Similarly, D_4 receptor agonist PD168077 (25 – $50 \mu\text{M}$) did not alter sIPSC frequency (Fig. 8B,

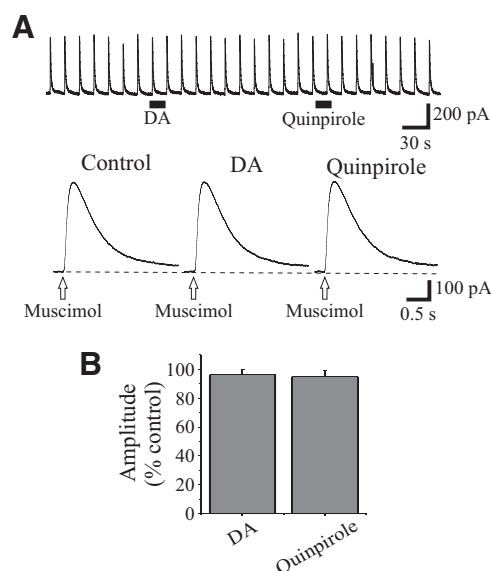


FIG. 7. DA does not alter postsynaptic GABA_A receptor mediated currents in TRN neurons. *A*: current recording from a TRN neuron showing repeatable outward response to focal pressure application of GABA_A receptor agonist muscimol ($50 \mu\text{M}$, 50 ms). Bath application of either DA ($25 \mu\text{M}$) or quinpirole ($10 \mu\text{M}$) did not alter the muscimol-mediated outward currents. Representative examples are shown below. *B*: population data illustrating amplitude of the muscimol-induced currents following DA ($n = 3$) or quinpirole ($n = 6$) exposure.

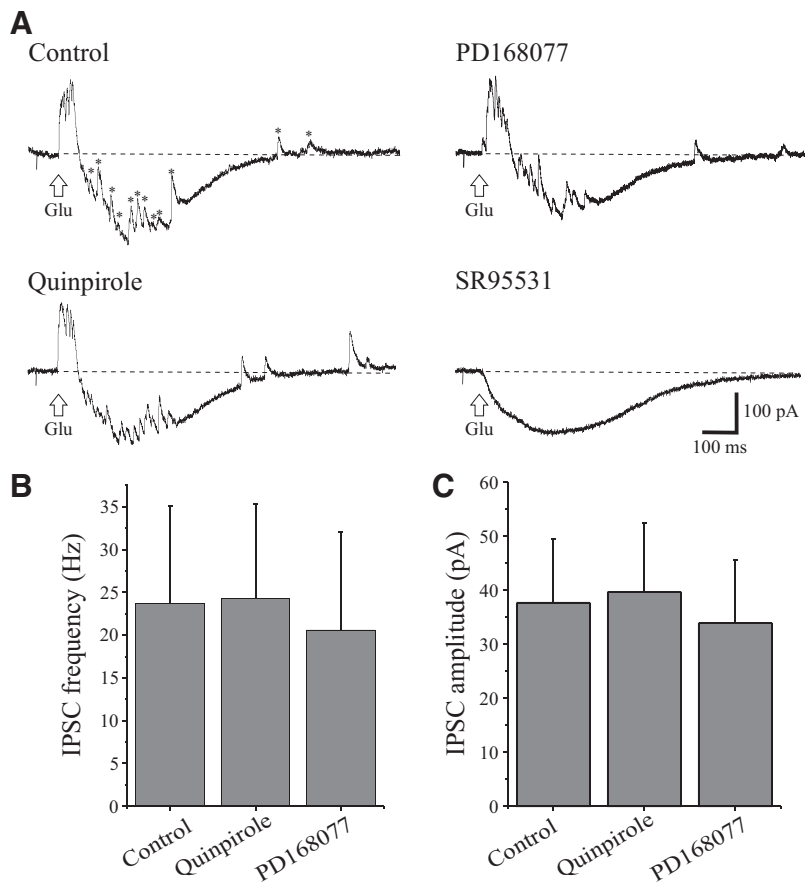


FIG. 8. Activation of DA receptors does not alter intra-TRN inhibition. **A**: current recording from a TRN neuron reveals that focal glutamate application via pressure ejection within TRN ($500 \mu\text{M}$, 50 ms , 30 s interval) elicits short outward current and long-lasting inward current along with increase in spontaneous IPSCs (sIPSCs, *). After repeating this several times, either quinpirole ($10 \mu\text{M}$) or PD168077 ($50 \mu\text{M}$) was bath applied (45 s). The sIPSCs evoked by glutamate application are not altered by the DA agonists. Subsequent application of GABA_A receptor antagonist SR95531 ($10 \mu\text{M}$) completely blocked sIPSCs. **B** and **C**: population data indicating no significant change in sIPSC frequency (**B**) or sIPSC amplitude (**C**) by quinpirole or PD168077.

control: $23.3 \pm 12.7 \text{ Hz}$, PD168077: $20.6 \pm 11.5 \text{ Hz}$, $n = 5$, $P = 0.1$). Likewise sIPSC amplitudes were also unaltered by either quinpirole (control: $37.7 \pm 11.8 \text{ pA}$, quinpirole: $39.7 \pm 12.8 \text{ pA}$, $n = 5$, $P = 0.9$) or PD168077 (Fig. 8C, control: $35.9 \pm 12.3 \text{ pA}$, PD168077: $33.9 \pm 11.7 \text{ pA}$, $n = 5$, $P = 0.4$). The data suggests that the DA-mediated reduction in inhibitory synaptic transmission in TRN neurons is limited to the GP-TRN inhibition and not intra-TRN inhibition.

DISCUSSION

We demonstrate that the activation of presynaptic D₄ receptors selectively suppresses GABA_A receptor-mediated inhibition at pallido-thalamic innervation without altering intra-TRN inhibition (Fig. 7). The reduction in GP-thalamic inhibition is by reducing GABA release at presynaptic terminals of GP neurons via D₄ receptor activation. Despite the recognized association of D₄ receptors with schizophrenia, attention deficit hyperactivity disorder, and other mental disorders (Oak et al. 2000; Seeman et al. 1993), the cellular mechanisms by which D₄ receptors modulate neuronal functions remain elusive. Anatomical studies have shown that D₂-like dopamine receptors are expressed by GABAergic neurons including TRN and GP (Khan et al. 1998; Mrzljak et al. 1996); however, their functional role on inhibitory synaptic transmission has not been explored.

TRN receives GABAergic projections from GP, SNr, and basal forebrain (Anaya-Martinez et al. 2006; Asanuma 1994; Asanuma and Porter 1990; Bickford et al. 1994). In addition, TRN neurons form intra-TRN connections via axon collaterals

(Huntsman et al. 1999; Shu and McCormick 2002). Although the precise origin of GABA terminals within the TRN containing the D₄ receptors remains unclear, GP neurons have been shown to express D₄ receptor and its mRNA (Ariano et al. 1997; Defagot et al. 1997; Mrzljak et al. 1996). Anatomical evidence suggests that TRN neurons receive dopaminergic innervations from substantia nigra pars compacta (Anaya-Martinez et al. 2006; Garcia-Cabezas et al. 2007, 2009; Sanchez-Gonzalez et al. 2005) and expresses DA receptors (Ariano et al. 1997; Defagot et al. 1997; Khan et al. 1998; Mrzljak et al. 1996). In this study, we have demonstrated a functional role of D₄ receptors exclusively found on GABAergic neurons (Mrzljak et al. 1996). Our present findings are supported by a evidence suggesting that the activation of D₄ receptors can modulate GABA release in TRN (Floran et al. 2004).

The dopaminergic system in TRN is thought to play crucial role in sensory gating and has been postulated that some of the manifestations of disorders of dopaminergic transmission may be caused by abnormal TRN function. For example, the TRN plays a central role in the control of attention (Guillery et al. 1998; Mayo 2009; McAlonan et al. 2008; Rees 2009; Yu et al. 2009), and attention deficit hyperactive disorder (ADHD) is associated with genetic abnormalities of dopamine D₄ receptors (Castellanos and Tannock 2002; LaHoste et al. 1996). Moreover, TRN lies at the interface of thalamocortical circuits between prefrontal cortex and associated thalamic relay nuclei, thus alterations in TRN signaling will influence the gating properties between these two structures, which could underlie

the hypothesized role of TRN in attention mechanisms (Zikopoulos and Barbas 2006). Additionally, abnormal dopaminergic function in the TRN may also contribute to some of the manifestations of Parkinson's disease, such as the sleep disorders (Rye and Jankovic 2002) and the abnormal processing of proprioceptive signals (Dietz 2002). By its connections with motor-related structures, TRN is thought to play integrative role in motor functions (Anaya-Martinez et al. 2006; Kane et al. 2009; Obeso et al. 2008; Piggott et al. 2007). Thus alterations in dopaminergic system in TRN may lead to abnormal motor functions found in Parkinson's disease. In fact, the D₄ receptor-containing GABAergic neurons of the SNr and GP are thought to constitute major links in the basal ganglia loop circuits that regulate the motor thalamus and the cortex in sequence. We propose that activation of SNc neurons leads to release of DA in TRN, and this in turn activates D₄ receptor on GP terminals leading to reduced GABA release. The reduced inhibition by activation of SNc neurons may lead to increased excitability of TRN neurons and decrease in output of thalamocortical neurons. Thus activation of D₄ receptor can influence the thalamocortical circuit activity.

Thalamic inhibitory mechanisms have been shown to play crucial role in thalamocortical oscillations associated with arousal and sleep mechanisms (Huguenard and McCormick 2007; McCormick and Bal 1997; Sohal et al. 2000, 2003; Steriade 1992, 1997; vonKrosigk et al. 1993). Schizophrenic patients have been reported to show abnormalities in slow-wave sleep that are correlated with the state of spindle activity and synchronization of cortical and thalamic activity (Keshavan et al. 1995). Thus thalamic D₂-like receptors are thought to play key roles in pathophysiology of schizophrenia (Buchsbbaum et al. 2006). Elevated levels of D₄ receptors have been reported in schizophrenics (Seeman et al. 1993). In addition, alterations in thalamic D₂ receptors have been reported in schizophrenia (Takahashi et al. 2006). Clearly there are a number of different alterations in thalamocortical activities that may result in alterations in sensory processing and attentional modulation, the underlying mechanisms leading to such alterations and further connection to the manifestation of specific schizophrenic behaviors remains speculative (Behrendt 2006). Nonetheless malfunctioning of DA receptors in TRN is one mechanism that would lead to abnormalities in thalamocortical rhythms and thalamic gating that could contribute to some symptoms of schizophrenia. Additional studies are required to further unravel the functional significance of DA in the thalamus under normal and pathological conditions such as schizophrenia.

ACKNOWLEDGMENTS

We thank R. and L. Peterson (Sunshine from Darkness Gala) for their generous donation to the National Alliance for Research on Schizophrenia and Depression, which helped in carrying out this work.

GRANTS

This work was supported by funding from the National Eye Institute to C. L. Cox and from the National Alliance for Research on Schizophrenia and Depression to G. Govindaiah.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES

- Anaya-Martinez V, Martinez-Marcos A, Martinez-Fong D, Aceves J, Erij D.** Substantia nigra compacta neurons that innervate the reticular thalamic nucleus in the rat also project to striatum or globus pallidus: implications for abnormal motor behavior. *Neuroscience* 143: 477–486, 2006.
- Ariano MA, Wang J, Noblett KL, Larson ER, Sibley DR.** Cellular distribution of the rat D-4 dopamine receptor protein in the CNS using anti-receptor antisera. *Brain Res* 752: 26–34, 1997.
- Asanuma C.** Gabaergic and pallidal terminals in the thalamic reticular nucleus of squirrel monkeys. *Exp Brain Res* 101: 439–451, 1994.
- Asanuma C, Porter LL.** Light and electron-microscopic evidence for a GABAergic projection from the caudal basal forebrain to the thalamic reticular nucleus in rats. *J Comp Neurol* 302: 159–172, 1990.
- Behrendt RP.** Dysregulation of thalamic sensory “transmission” in schizophrenia: neurochemical vulnerability to hallucinations. *J Psychopharmacol* 20: 356–372, 2006.
- Bickford ME, Gunluk AE, Vanhorn SC, Sherman SM.** Gabaergic projection from the basal forebrain to the visual sector of the thalamic reticular nucleus in the cat. *J Comp Neurol* 348: 481–510, 1994.
- Buchsbbaum M, Christian B, Lehrer D, Narayanan T, Shi B, Mantil J, Kemether E, Oakes T, Mukherjee J.** D₂/D₃ dopamine receptor binding with [³H]-[F-18]fallypride in thalamus and cortex of patients with schizophrenia. *Schizophrenia Res* 85: 232–244, 2006.
- Castellanos FX, Tannock R.** Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nat Rev Neurosci* 3: 617–628, 2002.
- Defagot MC, Malchiodi EL, Villar MJ, Antonelli MC.** Distribution of D₄ dopamine receptor in rat brain with sequence-specific antibodies. *Mol Brain Res* 45: 1–12, 1997.
- Deleuze C, Huguenard JR.** Distinct electrical and chemical connectivity maps in the thalamic reticular nucleus: potential roles in synchronization and sensation. *J Neurosci* 26: 8633–8645, 2006.
- Di Chiara G.** *Dopamine in the CNS*. Berlin: Springer, 2002.
- Dietz V.** Proprioception and locomotor disorders. *Nat Rev Neurosci* 3: 781–790, 2002.
- Floran B, Floran L, Erij D, Aceves J.** Activation of dopamine D₄ receptors modulates [H-3]GABA release in slices of the rat thalamic reticular nucleus. *Neuropharmacology* 46: 497–503, 2004.
- Gandia JA, Delasheras S, Garcia M, Gimenezamaya JM.** Afferent projections to the reticular thalamic nucleus from the globus pallidus and the substantia nigra in the rat. *Brain Res Bull* 32: 351–358, 1993.
- Garcia-Cabezas MA, Martinez-Sanchez P, Sanchez-Gonzalez MA, Garzon M, Cavada C.** Dopamine innervation in the thalamus: monkey versus rat. *Cereb Cortex* 19: 424–434, 2009.
- Garcia-Cabezas MA, Rico B, Sanchez-Gonzalez MA, Cavada C.** Distribution of the dopamine innervation in the macaque and human thalamus. *Neuroimage* 34: 965–984, 2007.
- Glase SA, Akunne HC, Georgic LM, Heffner TG, MacKenzie RG, Manley PJ, Pugsley TA, Wise LD.** Substituted [(4-phenylpiperazinyl)methyl]benzamides: selective dopamine D-4 agonists. *J Med Chem* 40: 1771–1772, 1997.
- Govindaiah G, Cox CL.** Excitatory actions of dopamine via D₁-like receptors in the rat lateral geniculate nucleus. *J Neurophysiol* 94: 3708–3718, 2005.
- Govindaiah G, Cox CL.** Depression of retinogeniculate synaptic transmission by presynaptic D-2-like dopamine receptors in rat lateral geniculate nucleus. *Eur J Neurosci* 23: 423–434, 2006a.
- Govindaiah G, Cox CL.** Metabotropic glutamate receptors differentially regulate GABAergic inhibition in thalamus. *J Neurosci* 26: 13443–13453, 2006b.
- Guillery RW, Feig SL, Lozsadi DA.** Paying attention to the thalamic reticular nucleus. *Trends Neurosci* 21: 28–32, 1998.
- Hazrati LN, Parent A.** Projection from the external pallidum to the reticular thalamic nucleus in the squirrel monkey. *Brain Res* 550: 142–146, 1991.
- Hughes SW, Cope DW, Blethyn KL, Crunelli V.** Cellular mechanisms of the slow (< 1 Hz) oscillation in thalamocortical neurons in vitro. *Neuron* 33: 947–958, 2002.
- Huguenard JR, McCormick DA.** Thalamic synchrony and dynamic regulation of global forebrain oscillations. *Trends Neurosci* 56, 2007.
- Huntsman MM, Porcello DM, Homanics GE, DeLorey TM, Huguenard JR.** Reciprocal inhibitory connections and network synchrony in the mammalian thalamus. *Science* 283: 541–543, 1999.
- Jones EG.** Some aspects of organization of thalamic reticular complex. *J Comp Neurol* 162: 285–308, 1975.

- Kane A, Hutchison WD, Hodaie M, Lozano AM, Dostrovsky JO. Dopamine-dependent high-frequency oscillatory activity in thalamus and subthalamic nucleus of patients with Parkinson's disease. *Neuroreport* 20: 1549–1553, 2009.
- Keshavan MS, Miewald J, Haas G, Sweeney J, Ganguli R, Reynolds CF. Slow-wave sleep and symptomatology in schizophrenia and related psychotic disorders. *J Psychiatric Res* 29: 303–314, 1995.
- Khan ZU, Gutierrez A, Martin R, Penafiel A, Rivera A, De La Calle A. Differential regional and cellular distribution of dopamine D2-like receptors: An immunocytochemical study of subtype-specific antibodies in rat and human brain. *J Comp Neurol* 402: 353–371, 1998.
- LaHoste GJ, Swanson JM, Wigal SB, Glabe C, Wigal T, King N, Kennedy JL. Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. *Mol Psychiatry* 1: 121–124, 1996.
- Lam YW, Nelson CS, Sherman SM. Mapping of the functional interconnections between thalamic reticular neurons using photostimulation. *J Neurophysiol* 96: 2593–2600, 2006.
- Lee SH, Govindaiah G, Cox CL. Heterogeneity of firing properties among rat thalamic reticular nucleus neurons. *J Physiol* 582: 195–208, 2007.
- Mayo JP. Intrathalamic mechanisms of visual attention. *J Neurophysiol* 101: 1123–1125, 2009.
- McAlonan K, Cavanaugh J, Wurtz RH. Guarding the gateway to cortex with attention in visual thalamus. *Nature* 456: 391–394, 2008.
- McCormick DA, Bal T. Sleep and arousal: thalamocortical mechanisms. *Annu Rev Neurosci* 20: 185–215, 1997.
- Mrzljak L, Bergson C, Pappy M, Huff R, Levenson R, GoldmanRakic PS. Localization of dopamine D4 receptors in GABAergic neurons of the primate brain. *Nature* 381: 245–248, 1996.
- Oak JN, Oldenhof J, Van Tol HHM. The dopamine D-4 receptor: one decade of research. *Eur J Pharmacol* 405: 303–327, 2000.
- Obeso JA, Rodriguez-Oroz MC, Benitez-Temino B, Blesa FJ, Guridi J, Marin C, Rodriguez M. Functional organization of the basal ganglia: therapeutic implications for Parkinson's disease. *Move Disorders* 23: S548–S559, 2008.
- Pare D, Hazrati LN, Parent A, Steriade M. Substantia-nigra pars reticulata projects to the reticular thalamic nucleus of the cat—a morphological and electrophysiological study. *Brain Res* 535: 139–146, 1990.
- Patel S, Freedman S, Chapman KL, Emms F, Fletcher AE, Knowles M, Marwood R, Mcallister G, Myers J, Curtis N, Kulagowski JJ, Leeson PD, Ridgill M, Graham M, Matheson S, Rathbone D, Watt AP, Bristow LJ, Rupniak NM, Baskin E, Lynch JJ, Ragan CI. Biological profile of L-745,870, a selective antagonist with high affinity for the dopamine D4 receptor. *J Pharmacol Exp Ther* 283: 636–647, 1997.
- Phillipson OT, Cornwall J, Jones MW, Kilpatrick IC. Thalamic control of dopamine function—a role for the reticular nucleus. *Biogenic Amines* 9: 395–402, 1993.
- Piggott MA, Ballard CG, Dickinson HO, McKeith IG, Perry RH, Perry EK. Thalamic D-2 receptors in dementia with Lewy bodies, Parkinson's disease, and Parkinson's disease dementia. *Int J Neuropsychopharmacol* 10: 231–244, 2007.
- Pinault D. The thalamic reticular nucleus: structure, function and concept. *Brain Res Rev* 46: 1–31, 2004.
- Rees G. Visual attention: the thalamus at the centre? *Curr Biol* 19:R213–R214, 2009.
- Rye DB, Jankovic J. Emerging views of dopamine in modulating sleep/wake state from an unlikely source: PD. *Neurology* 58: 341–346, 2002.
- Sanchez-Gonzalez MA, Garcia-Cabezas MA, Rico B, Cavada C. The primate thalamus is a key target for brain dopamine. *J Neurosci* 25: 6076–6083, 2005.
- Schofield CM, Kleiman-Weiner M, Rudolph U, Huguenard JR. A gain in GABA(A) receptor synaptic strength in thalamus reduces oscillatory activity and absence seizures. *Proc Natl Acad Sci USA* 106: 7630–7635, 2009.
- Seeman P, Guan HC, Vantol HHM. Dopamine D4 receptors elevated in schizophrenia. *Nature* 365: 441–445, 1993.
- Shu YS, McCormick DA. Inhibitory interactions between ferret thalamic reticular neurons. *J Neurophysiol* 87: 2571–2576, 2002.
- Shapiro MS, Wollmuth LP, Hille B. Modulation of Ca²⁺ channels by PTX-sensitive G-proteins is blocked by N-ethylmaleimide in rat sympathetic neurons. *J Neurosci* 14: 7109–7116, 1994.
- Silverman BD, Pitman MC, Platt DE, Rigoutsos I. Molecular moment similarity between clozapine and substituted [(4-phenylpiperazinyl)-methyl] benzamides: selective dopamine D4 agonists. *J Comput Aided Mol Design* 12: 525–532, 1998.
- Sohal VS, Huntsman MM, Huguenard JR. Reciprocal inhibitory connections regulate the spatiotemporal properties of intrathalamic oscillations. *J Neurosci* 20: 1735–1745, 2000.
- Sohal VS, Keist R, Rudolph U, Huguenard JR. Dynamic GABA(A) receptor subtype-specific modulation of the synchrony and duration of thalamic oscillations. *J Neurosci* 23: 3649–3657, 2003.
- Steriade M. Basic mechanisms of sleep generation. *Neurology* 42: 9–18, 1992.
- Steriade M. Synchronized activities of coupled oscillators in the cerebral cortex and thalamus at different levels of vigilance. *Cereb Cortex* 7: 583–604, 1997.
- Steriade M, McCormick DA, Sejnowski TJ. Thalamocortical oscillations in the sleeping and aroused brain. *Science* 262: 679–685, 1993.
- Takahashi H, Higuchi M, Suhara T. The role of extrastriatal dopamine D2 receptors in schizophrenia. *Biol Psychiatry* 59: 919–928, 2006.
- vonKrosigk M, Bal T, McCormick DA. Cellular mechanisms of a synchronized oscillation in the thalamus. *Science* 261: 361–364, 1993.
- Wang X, Zhong P, Yan Z. Dopamine D-4 receptors modulate GABAergic signaling in pyramidal neurons of prefrontal cortex. *J Neurosci* 22: 9185–9193, 2002.
- Werner P, Hussy N, Buell G, Jones KA, North RA. D-2, D-3, and D-4 dopamine receptors couple to G protein-regulated potassium channels in *Xenopus* oocytes. *Mol Pharmacol* 49: 656–661, 1996.
- Yan Z, Song WJ, Surmeier J. D2 dopamine receptors reduce N-type Ca²⁺ currents in rat neostriatal cholinergic interneurons through a membrane-delimited, protein-kinase-C-insensitive pathway. *J Neurophysiol* 77: 1003–1015, 1997.
- Yasuno F, Suhara T, Okubo Y, Sudo Y, Inoue M, Ichimiya T, Takano A, Nakayama K, Haildin C, Farde L. Low dopamine D-2 receptor binding in subregions of the thalamus in schizophrenia. *Am J Psychiatry* 161: 1016–1022, 2004.
- Yu XJ, Xu XX, He SG, He JF. Change detection by thalamic reticular neurons. *Nat Neurosci* 12: 1165–1171, 2009.
- Zikopoulos B, Barbas H. Prefrontal projections to the thalamic reticular nucleus form a unique circuit for attentional mechanisms. *J Neurosci* 26: 7348–7361, 2006.
- Zucker RS, Regehr WG. Short-term synaptic plasticity. *Annu Rev Physiol* 64: 355–405, 2002.