The laterodorsal tegmentum is essential for burst firing of ventral tegmental area dopamine neurons

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In response to behaviorally salient stimuli, dopamine (DA) neurons fire in bursts. Burst firing induces a large transient increase in synaptic DA and is regarded as the functionally relevant mode of transmission that signals reward and modulates goal-directed behavior. DA neuron burst firing is dynamically regulated by afferent inputs, and it is not present *in vitro* because of severing of afferent processes. However, what afferents are requisite for burst firing *in vivo* is not known. Here, we show that tonic input from the laterodorsal tegmental nucleus (LDTg) is required for glutamate-elicited burst firing in ventral tegmental area DA neurons of anesthetized rats. Also, after LDTg inactivation, DA neurons fire as they do *in vitro* (i.e., as pacemakers); even direct glutamate application fails to cause them to burst fire under these conditions. These data show that the LDTg is critical to normal DA function, and thus, pathology within this region may lead to aberrant DA signaling.

electrophysiology | laterodorsal tegmental nucleus | firing pattern | limbic system

Mesolimbic dopamine (DA) neurotransmission is mediated by the following two independent mechanisms: extrasynaptic (or "tonic") DA is mediated by basal DA neuron activity and regulated by presynaptic inputs, and transient (or "phasic") DA release is mediated by burst firing (1, 2). Thus, DA neuron burst firing induces a large transient increase in synaptic DA (3) and is considered to be the functionally relevant signal sent to postsynaptic sites to encode reward prediction or indicate incentive salience (1, 4–6).

DA neurons that are recorded *in vivo* typically display distinct patterns of activity, including an irregular firing rate ranging from 2 to 10 Hz (average, ≈4 Hz) with spontaneous burst events (7). The transition from irregular single-spike firing to burst firing depends on an excitatory amino acid because activation of glutamatergic afferents or direct microiontophoretic application of glutamate induces burst firing in DA neurons *in vivo* (2, 8, 9). Also, direct application of the competitive NMDA receptor antagonists (±)2-amino,5-phosphonopentanoic acid or (±)4-(3-phosphonopropyl)-2-piperazine carboxylic acid potently block spontaneous burst firing (10, 11). Therefore, NMDA receptor stimulation by glutamate has a primary role in regulating burst firing *in vivo*. However, glutamate alone is not sufficient to mediate burst firing. Thus, DA neurons recorded from mesencephalic slices obtained from adult rats, in which afferent input has been severed, display a regular pacemaker firing pattern (12) and cannot be made to fire in bursts in response to glutamate agonist administration or alterations in membrane potential (12–15).

There are several prominent inputs to the ventral tegmental area (VTA) that arrive from the tegmentum. The pedunculopontine tegmental nucleus (PPTg) is one such input, a glutamatergic/cholinergic neuronal group that has been shown to drive burst firing in VTA neurons (2, 16). Another input arises from the laterodorsal tegmental nucleus (LDTg) and associated CH6 cell group (17, 18). This input contains glutamate as well as cholinergic and GABAergic components, many of which are colocalized (19, 20). Given the significant and divergent afferent input from the PPTg and LDTg nuclei to the VTA and their potential role in the generation of burst firing, the aim of this study was to examine the effect of activation and inactivation of these afferent inputs on the activity of the population of DA neurons that are located in the VTA.

Results

The localization of injection sites throughout the mesopontine tegmentum are shown in Fig. 1. Modulation of the LDTg was done pharmacologically by drug infusion to provide a stable alteration in activity levels. The specificity and selectivity of infusions were shown by comparing the actions of NMDA or baclofen/muscimol with that of cholinergic agonists and antagonist that have been reported to modulate LDTg output by modulation of inhibitory autoreceptors (21, 22). Therefore, activation of M2-like receptors by the cholinergic agonist carbachol will decrease LDTg output and produce an effect equivalent to that produced by baclofen/muscimol-induced inactivation. Conversely, antagonism of tonically activated autoreceptors by the muscarinic receptor antagonist scopolamine will increase LDTg output, producing an effect that is equivalent to that produced by NMDA-induced activation.

Rats that received control vehicle infusions (0.5 μl of Dulbecco's PBS; $n = 6$ rats; 50 neurons) into the LDTg exhibited an average of 1.12 ± 0.1 spontaneously active DA neurons per electrode track that fired at an average rate of 4.5 ± 0.3 Hz and with 26 ± 4% of action potentials fired in bursts (Fig. 2 *A–C*), which is consistent with the findings in refs. 2 and 16. Intra-LDTg infusion of NMDA (0.75 μg per 0.5 μl; $n = 6$ rats; 78 neurons) or the muscarinic receptor antagonist scopolamine (50 μg per 0.5 μl; $n = 6$ rats; 71 neurons) to excite LDTg neurons resulted in a significant (≈2-fold; $P < 0.05$) increase in DA neuron population activity (defined as number of spontaneously active DA neurons observed per electrode track; Fig. 2*A*) without significantly affecting average burst firing or firing rate relative to control (Fig. 2 *B* and *C*).

Surprisingly, inactivation of the LDTg by coinfusion of the $GABA_A$ and $GABA_B$ agonists muscimol and baclofen, respectively (0.2 μg each per 0.5 μl; $n = 6$ rats; 52 neurons) or the cholinergic agonist carbachol (4 μg per 0.5 μl; $n = 6$ rats; 47 neurons) resulted in a small but significant reduction in firing rate (Fig. 2*B*) but a dramatic reduction in burst firing by 80–90% (Fig. 2*C*). After baclofen/muscimol inactivation of the LDTg, significant burst firing of midbrain DA neurons was observed only in 4 of 52 neurons. Also, the characteristics of the bursts remaining after baclofen/muscimol inactivation was altered in that there was a decrease in the average number of spikes per

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Abbreviations: DA, dopamine; ISI, interspike interval; LDTg, laterodorsal tegmental nucleus; PPTg, pedunculopontine tegmental nucleus; VTA, ventral tegmental area; A/P, anterior/posterior; PFC, prefrontal cortex.

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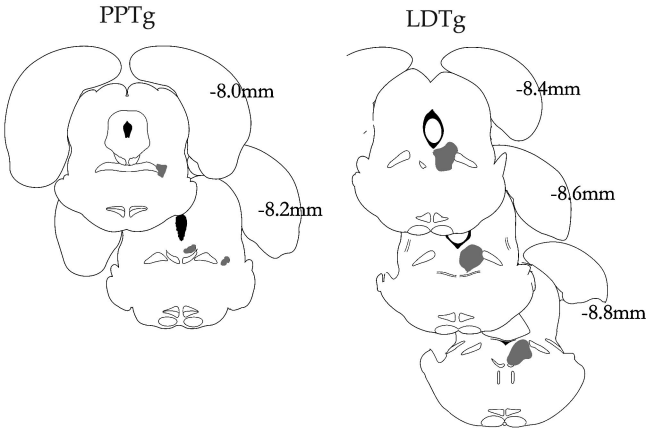

Fig. 1. Localization of cannula placements throughout the PPTg and LDTg. The shaded area represents the range of intracranial cannula tip placements. Numbers beside each plate represent the approximate A/P distance from bregma.

burst (control, 3.62 ± 0.04; baclofen/muscimol, 2.69 ± 0.07; $P < 0.05$). In addition to the changes in burst firing, DA neurons recorded after baclofen/muscimol administration showed a highly regular pacemaker-like firing pattern, which was defined by a significant decrease in the coefficient of variation (CoV) of the interspike interval (ISI) (CoV: control, 0.72 ± 0.06; baclofen/muscimol, 0.32 ± 0.03; $P < 0.05$) (Fig. 3). Pacemaker firing is commonly observed in DA neurons *in vitro*, but it is rarely observed *in vivo*.

Given the prominent role for glutamatergic transmission in the regulation of burst firing *in vivo*, we examined the effect of the simultaneous activation of the PPTg (a glutamatergic/cholinergic region that potently induces burst firing in VTA DA neurons) (2, 16) and LDTg inactivation. Activation of the PPTg by NMDA infusion (0.75 μg per 0.5 μl) reliably induces a substantial increase in burst firing (to ≈45%) (2, 16). However, after inactivation of the LDTg, activation of the PPTg ($n = 6$ rats; 48 neurons) failed to significantly affect any parameter of DA neuron activity compared with LDTg inactivation alone (Fig. 2*D*), suggesting that the decreased burst firing observed after LDTg inactivation is not simply a reflection of a decrease in glutamatergic tone.

Direct application of glutamate is known to potently increase DA neuron burst firing *in vivo* but not *in vitro*. During glutamate microiontophoresis (−2.5 to −40 nA), there was a substantial increase in the firing rate and burst firing of individual DA neurons recorded in control animals ($n = 6$ rats; 10 neurons; Fig. 4 *A* and *B*), which is consistent with the findings in ref. 9. After LDTg inactivation by baclofen/muscimol ($n = 11$; 26 neurons), the microiontophoretic application of glutamate still produced a significant increase in DA neuron firing rate with a similar potency to that seen in control animals (Fig. 4*C*). However, glutamate microiontophoresis did not increase burst firing in DA neurons after LDTg inactivation (Fig. 4*D*). Results are summarized in histogram form in Fig. 4 *E* and *F*. It is important to note that burst firing was observed/induced in 3 of 26 neurons, which is consistent with the number of neurons exhibiting baseline bursting after LDTg inactivation alone. Control application of saline (−10 nA) did not significantly alter DA neuron

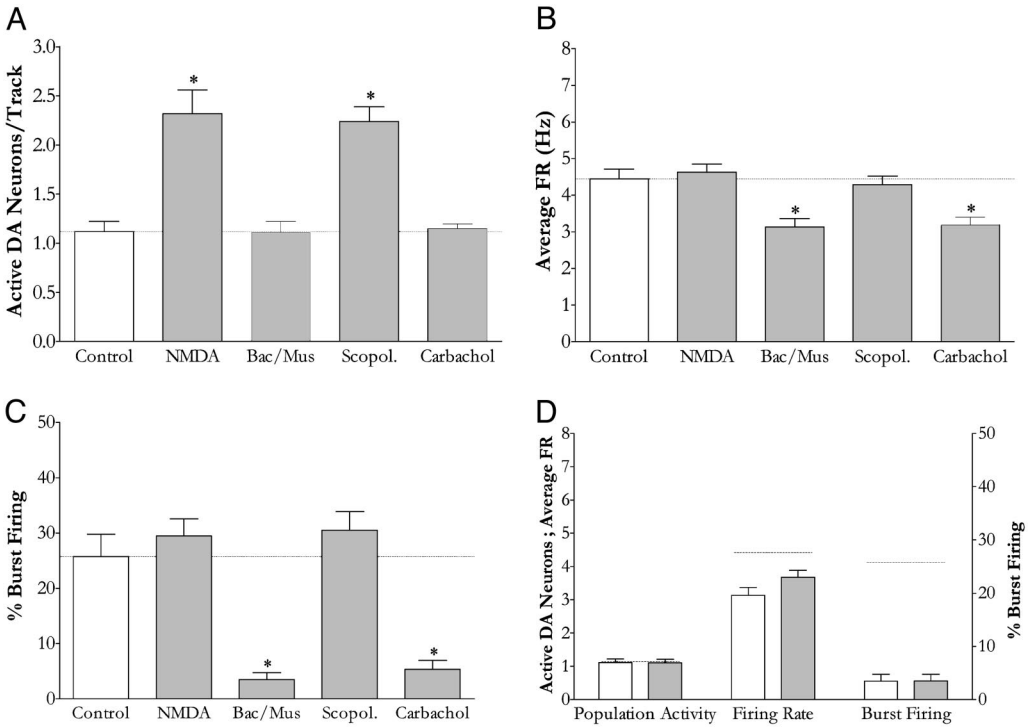

Fig. 2. LDTg manipulations alter the activity states of VTA DA neurons. NMDA (0.75 μg per 0.5 μl), baclofen/muscimol (0.2 μg each per 0.5 μl), carbachol (4 μg per 0.5 μl), scopolamine (50 μg per 0.5 μl), or vehicle (Dulbecco's PBS) were injected into the LDTg, and the activity of spontaneously active VTA DA neurons was examined. (*A–C*) The following three parameters of activity were recorded: population activity (number of spontaneously firing DA neurons per electrode track) (*A*), average firing rate (*B*), and average percentage of spikes fired in bursts (*C*). LDTg activation was found to increase population activity without affecting firing rate or burst firing; however, inactivation of the LDTg decreased firing rate and potently attenuated burst firing. (*D*) Activation of the PPTg by NMDA, which was found previously to potently increase burst firing, failed to alter any of these parameters after LDTg inactivation (filled bars) compared with LDTg inactivation alone (open bars). Horizontal lines represent control (vehicle infusions). *, $P < 0.05$, compared with control (vehicle infusions) by one-way ANOVA (Holm–Sidak post hoc test; $n = 6$ rats per group).

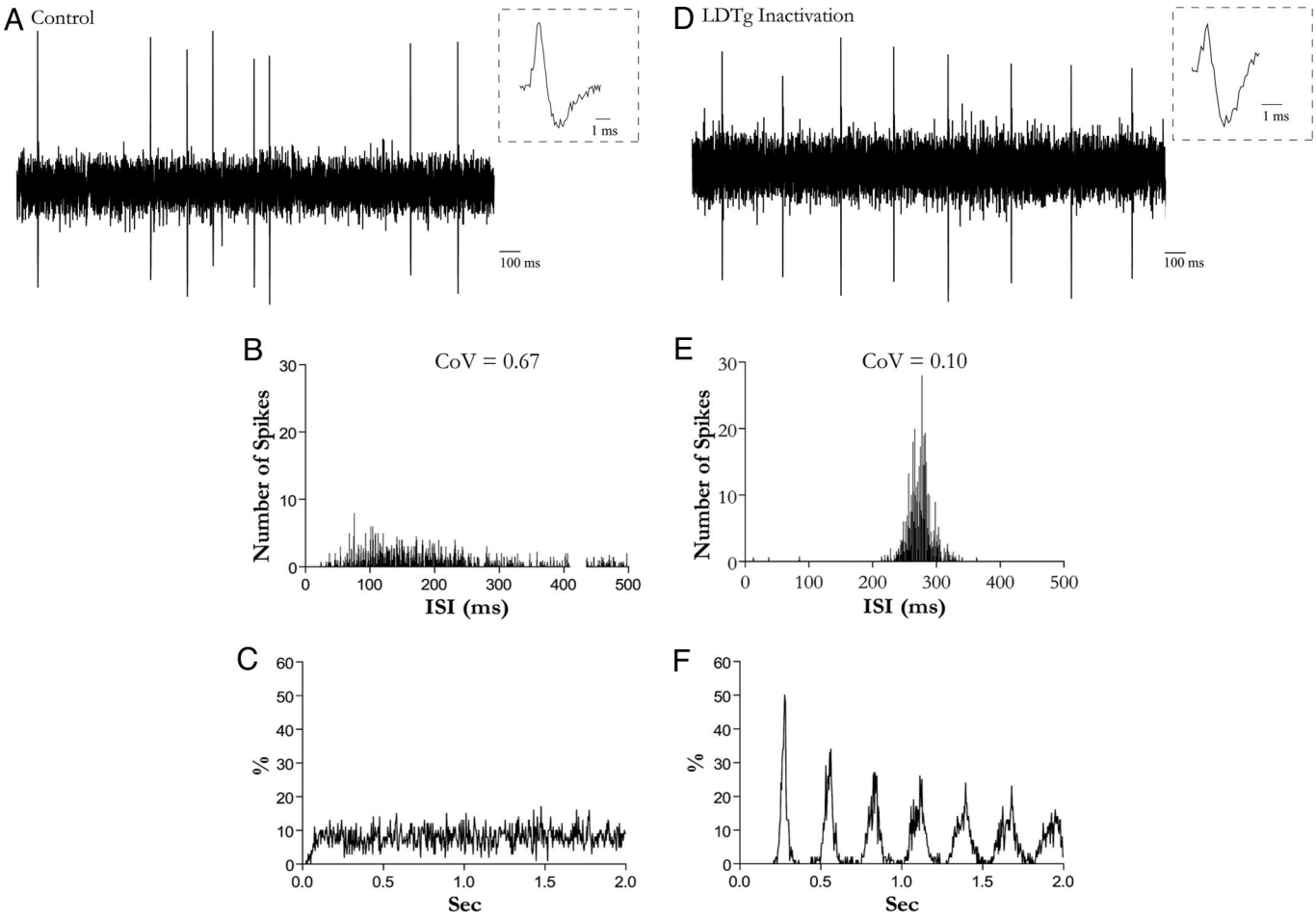

Fig. 3. Inactivation of the LDTg by baclofen/muscimol causes a regularization in the firing pattern of DA neurons recorded in the VTA. (*A–C*) In the control, DA neurons recorded *in vivo* typically display an irregular spontaneous firing pattern (*A*), as shown by the variable ISI histogram (*B*) and lack of peaks in the corresponding autocorrelogram (*C*). (*D–F*) After baclofen/muscimol inactivation of the LDTg, DA cells display a pattern of activity that is not usually observed *in vivo*, which is a significantly more regular, pacemaker-like pattern (*D*), as shown by a uniform distribution of the ISI histogram (*E*) and regularly occurring peaks in the autocorrelogram (*F*).

firing in either control or LDTg-inactivated rats (data not shown; $P > 0.05$).

Discussion

This study shows that the LDTg dynamically regulates both tonic DA neuron population activity as well as enabling glutamatergic inputs to drive burst firing in VTA DA neurons. Thus, activation of the LDTg by infusions of either the excitatory amino acid NMDA or the muscarinic receptor antagonist scopolamine promoted a significant increase in the number of spontaneously active DA neurons (population activity), whereas it had no effect on average firing rate or bursting activity. In contrast, inactivation of the LDTg with baclofen/muscimol or carbachol essentially eliminated spontaneous as well as afferent-induced (PPTg) and glutamate-induced (local) DA neuron burst firing without affecting population activity. After LDTg inactivation, DA neurons exhibited properties similar to those observed *in vitro* (i.e., a highly regular, pacemaker firing pattern and an absence of spontaneous and glutamate-driven burst firing) (12). Neither simultaneous PPTg activation nor glutamate microiontophoresis stimulated burst firing in the majority of DA neurons after LDTg inactivation. Taking these data together, we propose that the LDTg regulates the long-term responsivity of the DA system to behaviorally salient afferent drive and as such may have a major role in both the normal function and pathology associated with DA-related behaviors.

As described above, LDTg activation by NMDA or scopolamine resulted in a ≈2-fold increase in the number of spontaneously active DA neurons observed per electrode track without affecting the percentage of burst firing or average firing rate. Given the robustness of the correlation between DA neuron population activity and extracellular DA efflux (2, 23), these data are consistent with previous reports that electrical stimulation of the LDTg significantly increases accumbal DA efflux as measured by chronoamperometry *in vivo* (24). Also, behavioral experiments show that unilateral intra-LDTg *N*-methylscopolamine (a quaternary derivative of scopolamine) increases spontaneous locomotion in rats (25). Therefore, these data suggest a dynamic role for the LDTg in the regulation of DA system responsivity and ascending DA neurotransmission.

In addition to regulating population activity, the most interesting aspect of the LDTg is its role in enabling DA neuron burst firing. This finding is consistent with recent behavioral evidence that demonstrates a drastically decreased spontaneous locomotor activity after excitotoxic lesions of the LDTg that closely resemble those observed after 6-hydroxy-DA lesions of the VTA/nucleus accumbens pathway (ref. 26; although see ref. 27). This attenuation of bursting was not due to an absence of glutamatergic input from the LDTg, because inactivation of the

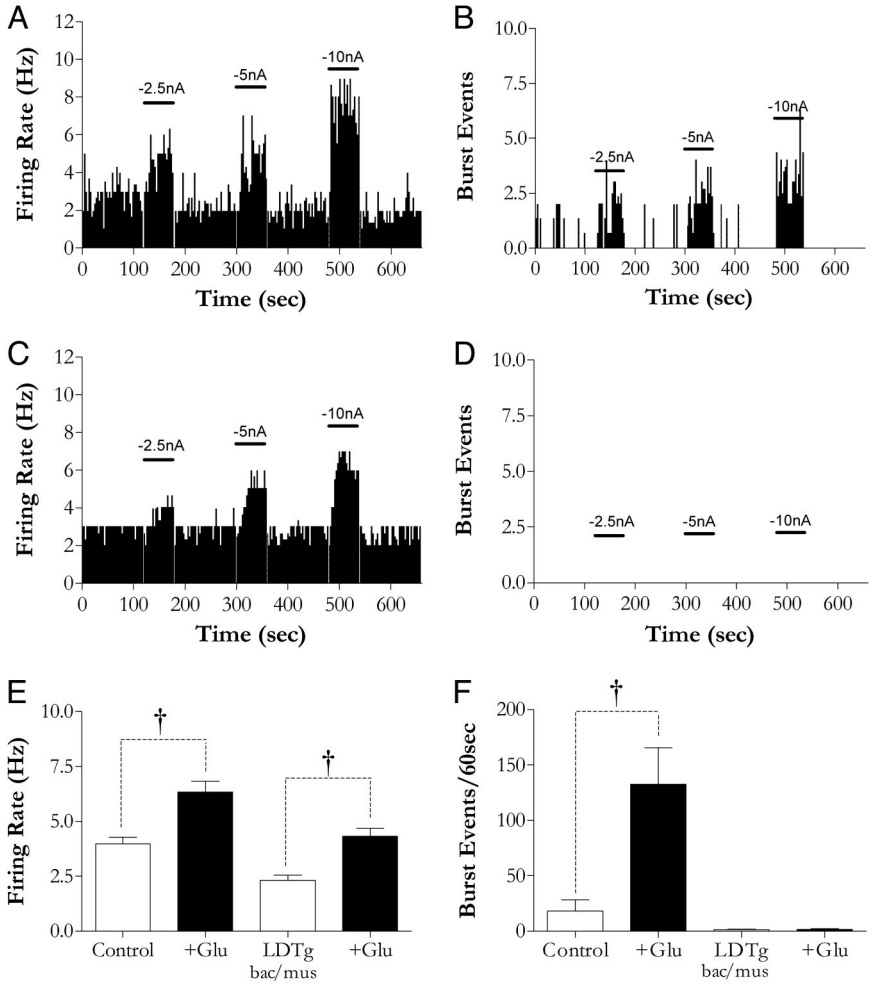

Fig. 4. Glutamate-induced burst firing is not present after LDTg inactivation. (*A* and *B*) Microiontophoretically applied glutamate resulted in a current-related increase in DA neuron firing rate (*A*) and burst firing (*B*) in control rats. (*C* and *D*) After LDTg inactivation by baclofen/muscimol, glutamate increased DA neuron firing rate (*C*) but did not significantly alter burst firing in most neurons (*D*). (*E* and *F*) Histograms represent group data from control ($n = 6$ rats; 10 cells) and LDTg-inactivated ($n = 11$ rats; 23 of 26 cells) rats, showing the effect of glutamate on average firing rate (*E*) or burst firing (*F*) before (open bars) and during (filled bars) glutamate microiontophoresis (−10 nA current). †, $P < 0.05$, compared with baseline, by paired *t* test.

LDTg prevented PPTg afferent-induced burst firing. The finding that LDTg activity is required to enable direct glutamate iontophoresis to elicit burst firing in DA neurons, without interfering with glutamate-induced increases in firing rate, was more striking. Thus, the LDTg appears to be the "other factor" that is required to enable glutamate to elicit burst firing in the intact preparation, and the absence of this input prevents glutamate alone from inducing burst firing *in vitro*.

The factor supplied by the LDTg to enable VTA DA neuron burst firing is unclear. It is known that the LDTg provides a significant cholinergic input to the VTA (17, 18), and recent findings suggest that midbrain muscarinic receptors contribute to the tonic excitatory regulation of accumbal DA transmission (28). Also, it has been suggested that acetylcholine released in the vicinity of midbrain DA neurons may permit burst firing by a Ca^{2+}-mediated decrease in gKCa (29, 30). However, microiontophoretically applied acetylcholine (or cholinergic agonists) (preliminary observations, $n = 4$ total neurons) onto identified DA neurons after baclofen/muscimol inactivation of the LDTg failed to induce a transition to a burst firing state. One potential caveat in this approach is that the direct, discrete application of cholinergic compounds may not necessarily replicate the cholinergic tone to the VTA. Also, the LDTg exhibits GABAergic afferents to DA neurons (19, 20) as well as varicosities containing dense-core vesicles, which may reflect the presence of neuropeptides (such as substance P) in this pathway (31, 32). The LDTg also innervates forebrain targets that may affect DA neuron activity. Given the complexity of the chemoarchitecture and anatomical connectivity of the LDTg, the specific transmitters that are associated with the decrease in DA neuron burst firing remain to be determined. However, the results from this study clearly show the importance of a tonic input from the LDTg in the regulation of DA neuron activity states. Also, because the LDTg receives a substantial input from the medial prefrontal cortex (PFC) (33), this region provides a powerful indirect means for the PFC to affect mesolimbic DA neuron activity, given the absence of a direct PFC–mesolimbic DA neuron projection (34). Such a link could provide a mechanism by which alterations in the PFC that are present in pathological states (such as schizophrenia, drug addiction, and affective disorders) (35–37) could lead to disruption of DA neuron signaling.

Together, these data show that the LDTg not only has the ability to dynamically regulate DA neuron population activity but also has an essential role in gating burst firing in most VTA DA neurons. After LDTg inactivation, DA neurons exhibited properties that are similar to DA neurons observed *in vitro* (i.e., a more regular, pacemaker firing pattern and an absence of spontaneous and glutamate-driven burst firing) (12). Therefore, we propose that the LDTg regulates the long-term responsivity

of the DA system. As a result, disruption within the LDTg or in its regulation by the PFC could be an underlying factor in the pathophysiology of major psychiatric disorders.

Materials and Methods

Animals and Surgery. All experiments were performed in accordance with the guidelines outlined in the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh. Male Sprague–Dawley rats (250–400 g) were anesthetized with chloral hydrate (400 mg/kg, i.p.) and placed in a stereotaxic apparatus. Chloral hydrate was used because under this anesthetic DA neuron activity states more closely resemble that observed in freely moving rats (38). Anesthesia was maintained by supplemental administration of chloral hydrate, as required to maintain suppression of limb compression withdrawal reflex, and a core body temperature of 37°C was sustained by a thermostatically controlled heating pad. For acute administration of drugs into discrete brain areas, rats were implanted with 23-gauge cannula at 2.0 mm dorsal to the LDTg [anterior/posterior (A/P), −8.3; medial/lateral (M/L), +0.6; dorsal/ventral (D/V), −4.5 mm from bregma] or dual 23-gauge cannula (tip separation approximately as follows: A/P, 0.5 mm; M/L, 1.0 mm; D/V, 0.5 mm] targeted 2 mm dorsal of the LDTg and PPTg (A/P, −8.0; M/L, +1.6; D/V, −5.0 mm from bregma) that were fixed in place with dental cement and two anchor screws.

Pharmacological Manipulations. Chemical stimulation was specifically used to enable neuronal excitation without the confounds associated with current spread, activation of fibers of passage, or potential lesions during extended stimulation that may occur with electrical activation. Only one injection was made into each brain region, and individual drug manipulations were performed in separate animals. All drugs were dissolved in Dulbecco's PBS and infused over ≈30 s in a volume of 0.5 μl through a 30-gauge injection cannula protruding 2.0 mm past the end of the implanted guide cannula. The injection cannula was left *in situ* for 1–2 min to ensure diffusion of drug into the surrounding tissue. The drugs used NMDA (0.75 μg per 0.5 μl) (2), a combination of the $GABA_A$ and $GABA_B$ agonists baclofen and muscimol (0.2 μg each per 0.5 μl) (2), the competitive nonselective muscarinic receptor antagonist scopolamine (50 μg per 0.5 μl) (39), the nonselective cholinergic agonist carbachol (4 μg/0.5 μl) (39), or vehicle (Dulbecco's PBS) were all injected at doses that have been reported to induce specific behavioral and/or neurochemical effects. The specificity and selectivity of infusions were shown by comparing the actions of NMDA or baclofen/muscimol with that of cholinergic agonists and antagonist that have been reported to modulate LDTg output by modulation of inhibitory autoreceptors (21, 22).

Extracellular Recordings. Glass extracellular microelectrodes (impedance, 6–14 MΩ) were lowered into the VTA (A/P, −5.3; medial/lateral, +0.8 mm from bregma and −6.5 to −9.0 mm ventral of brain surface) by using a hydraulic microdrive and the activity of the population of DA neurons was determined by counting the number of spontaneously active DA neurons encountered while making five to nine vertical passes (separated by 200 μm) in a predetermined pattern to sample equivalent regions of the VTA. Spontaneously active DA neurons were identified with open-filter settings (low pass, 50 Hz; high pass, 16 kHz) by using the electrophysiological criteria established in ref. 7, and, when isolated, their activity was recorded for 2–3 min. The three parameters of activity that were measured were (*i*) population activity (defined as the number of spontaneously active DA neurons recorded per electrode track), (*ii*) basal firing rate, and (*iii*) the proportion of action potentials occurring in bursts (defined as the occurrence of two spikes with an ISI of <80 ms, and the termination of the burst defined as the occurrence of an ISI of >160 ms) (9).

Microiontophoresis. Glutamate was applied directly by microiontophoresis to identified DA neurons to examine its ability to induce burst firing, as reported in ref. 9. Microiontophoresis was performed as reported in ref. 9. In brief, microiontophoretic electrodes were pulled from five-barrel glass micropipettes, and the center barrel was filled with 2 M NaCl containing Pontamine sky blue dye and used for extracellular recordings. The outer barrels were filled with 2 M NaCl (for automatic current balancing), 10 mM glutamate (in 150 mM NaCl, pH 8.0), or saline (150 mM, pH 8.0). Glutamate was retained with positive current (+5 to +10 nA) and ejected as an anion by using currents ranging from −2.5 to −40 nA.

Histology. At the cessation of the experiment, the recording site was marked by iontophoretic ejection of Pontamine sky blue from the tip of the recording electrode (−30 μA, constant current; 20–30 min). After dye injection, rats were killed by an overdose of anesthetic, decapitated, and their brains were removed, fixed for ≥48 h (8%, wt/vol, paraformaldehyde in PBS), and cryoprotected (25%, wt/vol, sucrose in PBS) for ≥24 h. Brains were sectioned (60-μm coronal sections), mounted onto gelatin–chrom alum-coated slides, and stained with Cresyl violet for histochemical verification of electrode sites and cannula sites. For experiments using dual cannulae, Pontamine sky blue (1% − 0.5 μl) was injected into the LDTg and Fast Green (1% − 0.5 μl) was injected into the PPTg immediately before decapitation to help localize placements. All histology was performed with reference to a stereotaxic atlas (40). The localization of injection sites throughout the LDTg and PPTg are shown in Fig. 1.

Analysis. Electrophysiological analysis of DA neuron activity was performed by using custom-designed computer software (NEUROSCOPE). All data are represented as the mean ± SEM unless otherwise stated. All statistics were calculated by using the SIGMASTAT software program (Jandel, San Rafael, CA).

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