

Excitatory Response of Prefrontal Cortical Fast-Spiking Interneurons to Ventral Tegmental Area Stimulation In Vivo

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ABSTRACT Prefrontal cortical (PFC) pyramidal neurons (PN) and fast spiking interneurons (FSI) receive dopaminergic (DA) and non-DA inputs from the ventral tegmental area (VTA). Although the responses of PN to VTA stimulation and DA administration have been extensively studied, little is known about the response of FSI to mesocortical activation. We explored this issue using single and double in vivo juxtacellular recordings of medial PFC PN and FSI with chemical VTA stimulation. Electrophysiological characteristics combined with Neurobiotin staining and parvalbumin immunohistochemistry allowed identification of recorded cells as FSI or PN. NMDA injection into the VTA increased firing in all FSI tested ($n = 7$), whereas most PN (7/11) responded with an inhibition. Furthermore, FSI excitation matching the temporal course of PN inhibition was observed with FSI–PN paired recordings ($n = 5$). These divergent electrophysiological responses to mesocortical activation could reflect PFC GABAergic interneurons contributing to silencing PN. Thus, the mesocortical system could provide a critical control of PFC circuits by simultaneously affecting FSI and PN firing. **Synapse 59:412–417, 2006.** © 2006 Wiley-Liss, Inc.

INTRODUCTION

The role of interneurons in shaping pyramidal neurons (PN) firing in diverse cortical circuits has been receiving increasing attention. For example, GABAergic interneurons are critical for rhythmic activity in distributed network of PN (Szabadics et al., 2001; Traub et al., 1996). These inhibitory neurons are connected via gap junctions (Galarreta and Hestrin, 2002), an arrangement that may account for their ability to become synchronized and modulate distributed arrays of neurons. In addition, many interneurons are reciprocally connected with PN (Bartho et al., 2004). The diverse populations of interneurons conform, with their interactions to PN, a local circuit that can shape the physiological outcome of the local network (Markram et al., 2004). Thus, the modulation of interneuron firing is likely to have a strong impact on cortical function (Buzsaki et al., 2004).

The role of interneurons in mesocortical function remains to be elucidated. The mesocortical projection originates in the ventral tegmental area (VTA) (Lindvall et al., 1974; Thierry et al., 1979) and employs do-

paminergic (DA) (Sesack et al., 1998) and GABA (Carr and Sesack, 2000; Steffensen et al., 1998) as its transmitters. This pathway is critical for several cognitive functions including decision-making, working memory, and attention (for review see Schultz, 2002). Although the DA modulation of PN in the prefrontal cortical (PFC) is relatively well understood (O'Donnell, 2003; Seamans and Yang, 2004), how this system affects interneurons is not known. Among GABA interneurons, parvalbumin-containing fast spiking interneurons (FSI) play a central role in determining the timing and spatial selectivity of PN firing (Rao et al., 2000). PFC FSI do express both D₁ and D₂ DA receptors (Le Moine

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and Gaspar, 1998; Mrzljak et al., 1996; Muly et al., 1998; Smiley et al., 1994; Vincent et al., 1993, 1995), suggesting that they are likely to be modulated by mesocortical activation. Indeed, anatomical data reveals that DA terminals contact GABA-containing neurons in the rat medial PFC (Benes et al., 1993; Sesack et al., 1995). In addition, recent *in vitro* electrophysiological studies revealed that the activity of FSI is strongly affected by DA (Gorelova et al., 2002; Tseng and O'Donnell, 2004). As interneurons do contact PN and mesocortical activation inhibits PFC cell firing (Lewis and O'Donnell, 2000; Pirot et al., 1992), it has been suggested that interneurons may be important in shaping the response of PN to VTA stimulation (O'Donnell et al., 2002; Tseng and O'Donnell, 2004). *In vivo* intracellular recordings from PFC PN assessing responses to bursts of VTA stimulation typically show a sustained membrane depolarization with suppression of cell firing (Lewis and O'Donnell, 2000) and a similar response had been observed with intra-PFC iontophoretic application of DA (Bernardi et al., 1982). As this suggests that a mesocortical, DA-dependent activation of interneurons may be responsible for this inhibition, we explored whether PFC FSI could be excited by VTA chemical activation and whether FSI responses matched changes in PN cell firing. We compared the effects of intra-VTA NMDA injection on FSI and PN action potential firing using juxtacellular recordings in the medial PFC of anesthetized animals.

METHODS

All experimental procedures were carried out according to the French (87-848, Ministère de l'Agriculture et de la Forêt) and the European Economic Community (86-6091, EEC) guidelines for care of laboratory animals. Animals were maintained on a 12:12 h light/dark cycle, with food and tap water available *ad libitum*, until the time of the experiment.

In vivo extracellular recordings of PFC neurons were performed in male adult Sprague-Dawley rats weighing 300–400 g, following the same experimental procedure described by Mallet et al. (2005). Briefly, rats were anesthetized with urethane (1.2–1.7 g/kg, *i.p.*), treated with a local anesthetic (lidocaine) on the scalp and pressure points, secured to a stereotaxic frame, and maintained at 37–38°C with a heating pad. A rat brain stereotaxic atlas (Paxinos and Watson, 2005) was used to guide electrode placement. Throughout the experiment, the level of anesthesia was determined by examining the tail pinch reflex. Additional urethane (0.25 g/kg, *s.c.*) was administered when necessary.

Extracellular single-unit activity was recorded with glass electrodes pulled from 1.5 mm o.d. borosilicate glass capillaries (GC150F, Harvard Apparatus, Edenbridge, England) using a Pull1 puller (WPI, Hertfordshire, England). The tip of the electrode was broken

under microscope to an external diameter of 1.2–1.4 μm , and filled with 0.4 M NaCl and 1% Neurobiotin (Vector Laboratories, Burlingame, CA). Electrodes had a resistance of 13–24 M Ω when measured *in vivo*. Neuronal activity was first amplified (10x; Axoclamp 2B, Axon Instruments, Foster City, CA), filtered (bandwidth: 300 Hz–10 kHz), and further amplified (100 times) with a differential AC amplifier (model 1700, A-M Systems, Carlsborg, WA, USA), sent to an A/D converter and acquired with a MacLab/4s system at a sampling rate of 20 kHz. The same output was also connected to a Window Discriminator (WPI) for spike detection. Spike occurrence was continuously recorded by a 1401plus CED system running Spike2.

The mesocortical projection was activated with intra-VTA NMDA injections. The pipette placement in the VTA was tested first by recording the DA metabolite DOPAC with voltammetry. A treated carbon fiber electrode was positioned above the VTA (5.1 mm caudal to bregma, 0.7 mm lateral to midline, and 7.0 mm from the cortical surface), and extracellular DOPAC was measured by differential normal pulse voltammetry (Svengningsson et al., 1999). The electrode was lowered in 250 μm steps while measuring DOPAC. Once a DOPAC signal was obtained, it was slowly advanced further to a spot yielding maximal DOPAC amplitude, which corresponds to the VTA core (Buda et al., 1981). The carbon fiber was then removed and a glass pipette filled with NMDA (100 μM) (Suaud-Chagny et al., 1992) was lowered into the selected site. The responses to NMDA injection were examined with extracellular recordings from both FSI and PN. The isolated unit was monitored for at least 5–10 min to assure stability of its firing rate, firing pattern, and spike waveform, and then 5 min of spontaneous baseline activity were recorded prior to delivering NMDA (70–100 nl over 10 s) into the VTA. Following NMDA injection, spontaneous activity was collected for 5–10 min. All changes in firing rate and pattern were investigated offline, comparing activity before (baseline) and after NMDA administration.

Recorded PFC neurons were juxtacellularly labeled with Neurobiotin as described elsewhere (Mallet et al., 2005; Pinault, 1996). Briefly, positive current pulses (2–6 nA, 250 ms) were applied at 2 Hz. The current was slowly increased until it drove cell firing for at least 10 min. At the end of the experiment and before perfusion, Pontamine Sky Blue (Interchim, Montluçon, France) was injected in four sites of a coronal plane 200 μm rostral to the recorded site. These additional injections were used as visual landmarks during the slicing procedure to optimize identifying the recorded cell placement. Rats were perfused with 300 ml saline (0.9% NaCl) followed by 200 ml of 4% paraformaldehyde, and brains were removed and kept overnight in 4% paraformaldehyde. Serial sections (40 μm -thick) were obtained starting from the blue landmarks up to

1 mm caudally, collected in PBS 0.1 M, and transferred into 30% sucrose in PBS for at least 1 h. To facilitate antibody penetration, all sections were flash-frozen in isopentane at -40°C , and immediately transferred to PBS. Following 1 h of pretreatment in PBS + 0.3% triton + 3% normal goat serum, all free-floating sections were incubated overnight at room temperature with Alexa 568-conjugated streptavidin (1:800, Molecular Probes, USA) and a monoclonal mouse anti-parvalbumin antibody (1:10,000, Swant, Switzerland) in PBS + 0.3% triton. After rinsing three times in PBS, the sections were incubated with a FITC-conjugated goat antimouse antibody at room temperature for 90 min (1:400 in PBS, Jackson Laboratories USA), rinsed again in PBS for another 30 min (3 times, 10 min), and mounted in Vectashield for microscopic fluorescent observation (Zeiss Axioplan 2).

Student's *t*-test was used for two-group comparisons involving a single continuous variable. The effects along two or more variables were compared using repeated measures ANOVA. If data were not normally distributed or had unequal variances, Kruskal-Wallis ANOVA by ranks was preferred for multiple comparisons involving interrelated proportions and the nonparametric Wilcoxon matched pair test was conducted for before and after treatment comparisons. Differences between experimental conditions were considered statistically significant when $P < 0.05$.

RESULTS

Juxtacellular recordings were conducted from 11 electrophysiologically identified FSI and 16 PN located in deep layers of the medial PFC in 13 animals. FSI exhibited shorter duration action potentials (0.7 ± 0.1 ms, mean \pm SD; Fig. 1A) and higher firing rate (4.5 ± 2.1 Hz; Fig. 1B) than PN (1.4 ± 0.2 ms and 1.1 ± 0.8 Hz, $P < 0.0001$ and $P < 0.004$, Student's *t*-test, respectively). Neurons that exhibited action potentials of less than 0.85 ms duration were classified as FSI, whereas cells showing action potentials longer than 0.95 ms were considered PN (Mallet et al., 2005; Tierney et al., 2004). Five neurons identified electrophysiologically as FSI were successfully filled with Neurobiotin, and all of them were parvalbumin positive (Fig. 1C). In contrast, all six putative PN (action potential duration: 1.2–1.6 ms) successfully filled with Neurobiotin were parvalbumin negative (Fig. 1C). Thus, action potential duration can reliably distinguish PN and FSI.

Mesocortical activation exerted different effects on both PFC cell types. NMDA injection ($100 \mu\text{M}$, ~ 70 nl) into the VTA increased cell firing in all seven FSI tested from 3.6 ± 1.8 Hz (measured from 120 s baseline activity) to 8.5 ± 4.1 Hz (measured from the 90 s following chemical VTA activation, Figs. 2A and 2B; $P = 0.017$, Wilcoxon matched pair test). The response typically initiated in the first 10–30 s after NMDA injection, and lasted for 30–120 s (Fig. 2C). In contrast,

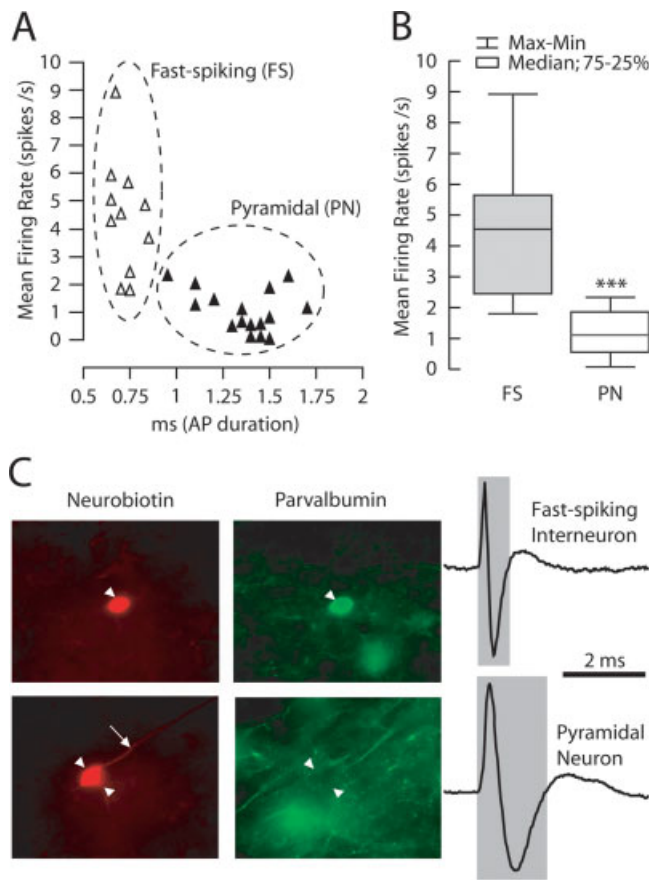


Fig. 1. Action potential duration and parvalbumin immunohistochemistry can distinguish FSI from PN. (A) Scatter plot showing the relationship between mean firing rate and action potential duration of all PN and FSI recorded in the medial PFC. Compared to PN, all FSI exhibited shorter action potentials (<0.85 ms). (B) Box-plot summarizing the data revealing that FSI are spontaneously more active compared to PN ($***P < 0.0005$, Kruskal-Wallis ANOVA by ranks). (C) Immunohistochemical identification of PFC FSI. Examples of a FSI (top panel) and a PN (bottom panel) labeled with Neurobiotin (left) showing their positive and negative immunoreactivity for parvalbumin (right), respectively. White triangles indicate the soma of the neurons; a white arrow points to the apical dendrite of the PN (bottom panel). Insets at right are action potential waveforms recorded from these two neurons. Traces are averages of several spikes and the measured duration is indicated by the grayed areas.

NMDA injection in the VTA decreased cell firing in 7 out of 11 PN (Figs. 2A and 2B), and had no effect in the remaining four, reducing the average firing rate from 1.0 ± 0.5 Hz to 0.6 ± 0.5 Hz ($P = 0.007$, Wilcoxon matched pair test, $n = 11$).

To examine whether VTA-evoked FSI excitation and PN inhibition were temporally correlated, we simultaneously recorded pairs of FSI and PN in some experiments by lowering two juxtacellular electrodes in the medial PFC and injecting NMDA in the VTA. In all cases ($n = 5$), FSI excitation matched the time course of the inhibition shown by a neighboring PN (Fig. 3). These results indicate that mesocortical activation can drive PFC interneurons and silence PN with a similar temporal course.

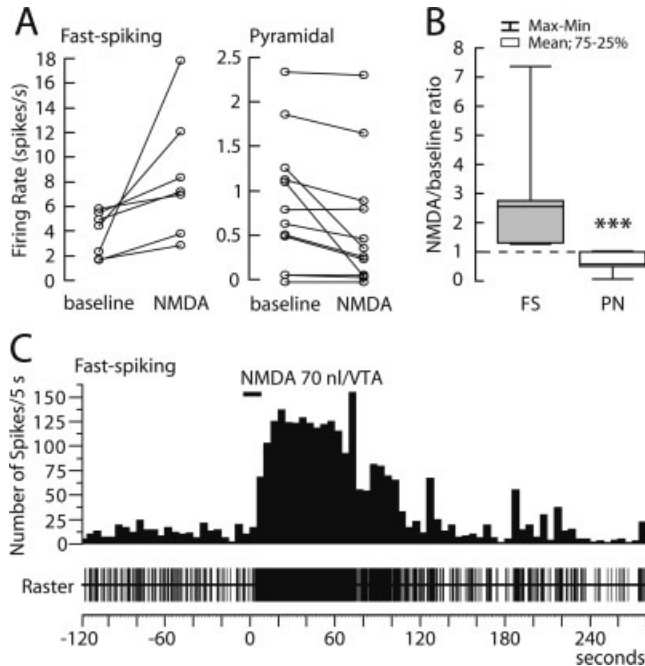


Fig. 2. Mesocortical activation exerts different effects on PFC, FSI, and PN. (A) Scatter plots showing effects of NMDA injection into the VTA on PFC FSI and PN firing. Open circles are data from individual neurons recorded from each group. VTA stimulation increased firing in all FSI and decreased firing in most PN recorded. (B) Box-plot summarizing differential responses of FSI and PN to VTA stimulation expressed as the ratio between firing rate during the 90 s following stimulation and the 120 s prior NMDA (** $P < 0.0007$, Kruskal–Wallis ANOVA by ranks). (C) Histogram and raster plot showing the time course of FSI responses to intra-VTA NMDA injection.

DISCUSSION

Juxtacellular recordings from PFC PN and FSI revealed different responses to mesocortical activation. Chemical VTA stimulation increased FSI cell firing and decreased activity in most PFC PN. When FSI and PN were recorded simultaneously, FSI increase was accompanied by a PN decrease firing. PN and FSI were identified according to action potential duration, as shown elsewhere (Mallet et al., 2005; Tierney et al., 2004). Combining Neurobiotin labeling and immunohistochemical staining further confirmed that FSI were parvalbumin-positive in all cases tested. This reinforces the notion that action potential duration is a reliable criterion to distinguish PN from FSI.

The inhibitory PN response observed in the present study is consistent with previous *in vivo* intracellular and extracellular data showing similar suppression of cell firing following electrical or chemical VTA stimulation (Ferron et al., 1984; Jay et al., 1995; Lewis and O'Donnell, 2000; Pirot et al., 1992). Several mechanisms could account for a VTA-induced inhibition. In fact, VTA stimulation may activate DA and/or GABA VTA projection neurons. Although GABA projection neurons include at least 50% of VTA cells (Carr and

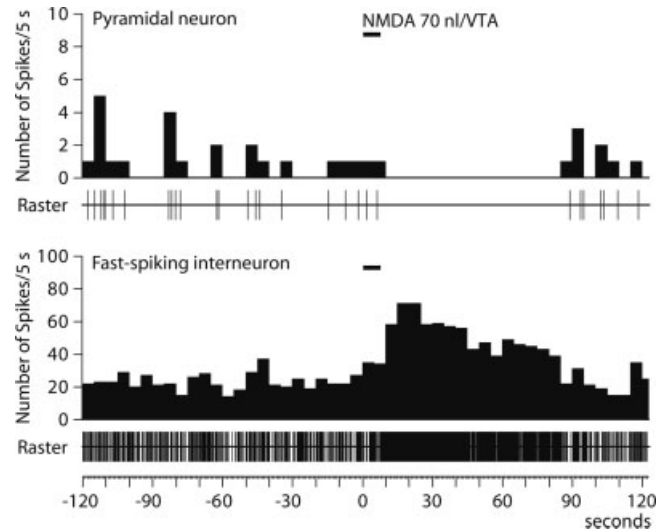


Fig. 3. PN and FSI responses exhibit similar temporal courses. Histograms show responses of a PN (top) and a FSI (bottom) recorded simultaneously in the medial PFC. Intra-VTA NMDA injection increased FSI and decreased PN firing with a similar duration.

Sesack, 2000; Steffensen et al., 1998), their cellular targets in the PFC are not clear. As they likely synapse on PN, a non-DA dependent inhibition resulting from activation of VTA GABA projection neurons may contribute to decrease PFC PN cell firing. Activation of mesocortical DA fibers could also mediate the inhibition of PN. Indeed, NMDA injection in the VTA induces DA cell burst firing and a marked increase in extracellular DA in the nucleus accumbens (Suaud-Chagny et al., 1992), suggesting that this procedure is also likely to raise DA levels in the PFC. Also, an early *in vivo* intracellular study showed that iontophoretic application of DA can elicit membrane potential depolarization and spike firing suppression in cortical PN (Bernardi et al., 1982). However, DA actions on PFC PN are complex and depend on the receptors activated. D_1 receptors increase PN excitability and enhance NMDA function through a postsynaptic PKA- and calcium-dependent mechanisms (Tseng and O'Donnell, 2004, 2005; Wang and O'Donnell, 2001), whereas D_2 receptors decrease PN excitability and attenuate both AMPA and NMDA-mediated excitation via several mechanisms including a direct postsynaptic modulation of intracellular signaling pathways and an indirect GABA-mediated inhibition (Tseng and O'Donnell, 2004). Therefore, the inhibitory response observed in PN following VTA stimulation could be due to DA acting directly on postsynaptic D_2 receptors or indirectly via activation of FSI, as well as to mesocortical GABA projection actions on PN.

FSI, on the other hand, were excited by mesocortical activation. Recent *in vitro* electrophysiological studies revealed that DA can exert a strong and sustained excitatory effect on PFC FSI. A D_1 -dependent FSI exci-

tation was observed in PFC brain slices obtained from prepubertal animals (Gorelova et al., 2002). In the adult brain, D₂ receptors also increase PFC FSI excitability in vitro (Tseng and O'Donnell, 2004) and elevate PFC GABA in vivo (Grobin and Deutch, 1998), suggesting that both D₁ and D₂ DA receptors could contribute to the enhanced FSI firing in response to mesocortical activation. There is also evidence suggesting that mesolimbic and mesocortical DA neurons can make functional glutamatergic connections with target neurons (Chuhma et al., 2004; Lavin et al., 2005; Sulzer et al., 1998). Although this issue remains controversial, a fast excitatory transmission could be required to initiate firing increase in FSI, which could be sustained by DA.

Mesocortical activation and its actions on persistent PFC activity have been associated with salient stimuli and working memory tasks (Goldman-Rakic, 1996). However, the mechanisms underlying these responses are not well understood. It has been proposed that the mesocortical system and in particular DA can support working memory and other cognitive functions by increasing detection of strong, behaviorally relevant signals, and reducing irrelevant activity (O'Donnell, 2003). In this regard, a modulation of the balance between PN and FSI firing in the PFC could be responsible for filtering of weak or irrelevant stimuli. As in other cortical regions (Somogyi and Klausberger, 2005; see review by Buzsaki et al., 2004), PFC FSI may shape the activity of PN networks and their responses to different inputs, including those arriving from the hippocampus (Tierney et al., 2004). Here, we observed that VTA stimulation increased FSI firing with a temporal course matching the inhibition in PN. Although it remains to be determined whether the PN inhibition is indeed mediated by FSI, it is tempting to speculate that a VTA-mediated excitation of FSI could modulate the timing and spatial selectivity of PN cell firing. With this combination of actions (i.e., direct inhibition by GABA projection cells, inhibition of PN by FSI, and complex excitation-inhibition effect of DA), the mesocortical system could promote synchrony in PN ensembles by sustaining up states (Lewis and O'Donnell, 2000; Tseng and O'Donnell, 2005) and limit the activation of inappropriate ensembles by actions on FSI.

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