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Strong Somatic stimulation differentially regulates the firing properties of prefrontal cortex neurons

Lourdes Nogueira[1] and **Antonieta Lavin**[1]

[1] Dept. of Neuroscience, Medical University of South Carolina, Charleston, SC, USA

Abstract

Among the brain structures involved in processing affective stimuli, the roles of the prefrontal cortex (PFC) and the mesocorticolimbic dopaminergic (DA) innervation are well established. In contrast to our understanding of the reward stimuli, less is known about how strong somatic stimulation is processed within the PFC. Here, we examined the effects of a strong pinch delivered to the rat posterior paw on spontaneous and current-evoked activity of PFC neurons using intracellular recordings in anesthetized rats. Following the paw pinch, pyramidal cells exhibited a significant decrease in spontaneous activity along with a significant increase in the current-evoked firing. The increase in current-evoked firing elicited by the paw pinch was inversely correlated with the baseline firing rate. Systemic administration of a selective dopamine D2 receptor antagonist partially blocked the effects elicited by the paw pinch on cortical excitability, whereas systemic administration of a D1 antagonist seems to facilitate paw-mediated increases in evoked firing. These results suggest that strong somatic stimuli decrease spontaneous firing while increasing depolarization-evoked firing in a DA receptor dependant manner. These mechanisms may help in the control of the signal to noise ratio or the salience of information processing in the PFC following strong somatic stimulation.

Keywords

cortical activity; intracellular recording; somatic stimuli; dopamine

Introduction

It is crucial for organisms to properly process appetitive and aversive stimuli. Without this ability organisms are unable to generate the proper sets of behaviors to either seek out rewards or avoid aversive stimuli. Among the many brain structures involved in processing rewarding and aversive stimuli, the role of the prefrontal cortex (PFC) has been well established (Becerra et al., 2001; Gootfried et al., 2002; O'Doherty, 2004; Kobayashi et al., 2006; Borsook et al., 2007). Dopamine (DA) also plays an important role in the processing of rewarding and aversive stimuli, but how DA release in the PFC correlates with the valence of an event is a matter of debate.

On the one hand, the PFC- DA system is exquisitely responsive to stress, for even mild stressors increase DA release in the PFC (Morrow et al., 2000a, b). Yet following a

Corresponding Author: Dr. Antonieta Lavin, Dept. of Neuroscience, MUSC, Phone: 843-792-6799, Fax: 843-792-4423, lavina@musc.edu.

rewarding event, DA levels also increase in the PFC (Feenstra and Botterblom 1996; Taber and Fibiger, 1997; Ahn and Phillips, 1999). Thus it appears that DA release in the PFC does not differentiate between the motivational valences of events, because similar increases in PFC DA occur as a consequence of both rewarding and aversive stimuli (Thierry et al, 1976; Abercrombie et al., 1989; Ljungberg et al., 1992; Horvitz et al., 1997; Wilkinson et al, 1998; Feenstra et al., 2001; Jackson and Moghaddam, 2004).

Although the levels of DA in the PFC increase following aversive stimuli, the firing of DAergic neurons in the ventral tegmental area (VTA) is usually reduced and the only VTA cells that show an increase in activity are non-dopaminergic cells (Ungless et al 2004). Likewise, DA neuron firing is reduced transiently either by negative reinforcement or the omission of an expected reward (Schultz, 1998; Ungless et al., 2004). At the level of the PFC, activation of the mesocortical DA system induces an inhibition of spontaneous firing of PFC neurons (Ferron et al., 1984). In contrast, some PFC cells are activated by aversive stimuli (Zhang et al., 2004; Kobayashi et al., 2006), and this response can be blocked by electric stimulation of the VTA (Mantz et al., 1988). In summary, both stress and aversive stimuli markedly increase PFC DA levels, as measured with microdialysis. Interestingly, both aversive stimuli and negative reinforcement reduce DA cell firing at the level of the VTA Therefore, it is unclear exactly how PFC neurons respond to stimuli of different valences, along with the extent of the mesocortical DA system's involvement.

We have previously shown that cells in the PFC respond to electrical stimulation of the VTA with a long-lasting increase in current-evoked excitability and a decrease in spontaneous activity (Lavin et al., 2005; Nogueira et al., 2006). However, the effects of aversive stimuli – such as a paw pinch – on PFC neuron firing are unknown. Using intracellular recordings in anesthetized rats we assessed the changes produced in current-evoked and spontaneous PFC firing following application of a strong somatic stimulus that has been previously shown to evoke decreases in the firing of DA cells in the VTA (mechanical pressure applied to the poster limb; Ungless et al., 2004). Given that our experiments were performed in anesthetized preparations, we are investigating the effects of somatic stimulation on PFC activity as opposed to the rat's affective response to an aversive stimulus. It is important to point out that previous studies have shown that anesthetized rats encode aversive, noxious stimulation (Zhang et al., 2004).

Our experiments found that strong somatic stimulation produce a small but significant increase in current-evoked firing and a small decrease in spontaneous firing in PFC neurons, akin to direct VTA stimulation. Moreover, cortical responses to 'paw pinch' appear to be principally affected by manipulation of DAD1 and DAD2 receptors.

Results

Effects of somatic stimulation on current-evoked firing of PFC neurons

A total of 32 cells were recorded from 16 Sprague-Dawley male rats. The cells had a baseline membrane potential of −68 ± 7.2 mV.

The effect of 'paw pinch' on the current-evoked activity of PFC cells located in layers V-VI was assessed in 18 neurons. Baseline recordings were taken for 10 minutes followed by application of mechanical pressure. The application of 'paw pinch' elicited a significant increase in the current-evoke firing of PFC cells (baseline: 5.2 ± 0.18 spikes/pulse; paw pinch: 7.0 ± 0.21 spikes/pulse, paired t-test $p < 0.0002$, n=18, Fig 1A, data were taken in bins of 1 sec every 30 sec and then averaged together for statistical comparison). The current-evoked data were recorded 30 sec after 'paw pinch', in bins of 1 sec every 30 sec. Consequently, the increase in current evoked excitability was detected in the first bin (30 sec

after paw pinch). Furthermore, the increase in current-evoked firing lasted for as long as the cells were held, on average 9 ± 2.0 minutes following the offset of the somatic stimuli.

The magnitude of the effect depended on the prevailing network conditions; specifically, whether the cell dynamically transitioned between up and down states.

Somatic stimuli had no effect on the current-evoked firing of cells with a bistable membrane potential at rest (12 of 18 cells; baseline: 5.5 ± 1.1 spikes/pulse; paw pinch: 5.7 ± 1.0 spikes/pulse, n=12, Figure 1B). In contrast non-bistable cells showed over a 100% increase in current-evoked firing following 'paw pinch' (6 of 18 cells; baseline: 4.2 ± 0.8 spikes/pulse; paw pinch: 8.8 ± 2.1 spikes/pulse, paired t-test $p < 0.0001$, n=6, Figure 1C). The change in magnitude in evoked firing was comparable to that observed following direct VTA stimulation (Lavin et al. 2005).

Cells that exhibited a lower baseline current-evoked firing also showed the largest increases in evoked firing following administration of strong somatic stimuli (Fig 1D). Thus, the increase in current-evoked firing was inversely correlated with the baseline firing rate (correlation coefficient = −0.46) ; particularly as cells transition between up and down states were more likely to fire at a higher rate in the baseline condition.

This effect may provide a means for increasing the signal response to a salient stimuli, as it is caused by current-evoked activity.

Dopamine receptor modulation of current-evoked firing following 'paw pinch

Systemic administration of the D2 receptor antagonist, sulpiride, blocked the increase in current-evoked excitability produced by 'paw pinch' (baseline: 4.5 ± 1.0 spikes/pulse; sulpiride: 5.0 ± 0.91 spikes/pulse; paw pinch: 5.0 ± 1.9 spikes/pulse, n=9, ANOVA $F[2,18] = 0.370$, $p < 0.69$, Fig 1E,). From 9 cells recorded, 5 were non-bistable and 4 were bistable (bistable cells: baseline: 5.5 ± 0.9 spikes/pulse; sulpiride: 4.1 ± 1.4 spikes/ pulse; paw pinch: 3.8 ± 0.2 spikes/pulse; non-bistable cells: baseline: 3.5 ± 0.6 spikes/pulse; sulpiride: 2.6± 0.4 spikes/pulse; paw pinch: 5.7 ± 1.5 spikes/pulse).

In contrast, D1 receptor blockade by systemic administration of SCH23390 failed to prevent the increase in current-evoked excitability following aversive stimuli (baseline: 4.8 ± 1.5 spikes/pulse; SCH 23390: 4.4 ± 1.7 spikes/pulse; paw pinch: 8.5 ± 3.4 spikes/pulse, ANOVA $F[2,54]=28.7$ $p < 0.001$, Fisher post-hoc test, $p<0.001$ n= 9, Fig 1F). Indeed, systemic administration of SCH 23390 decreased basal firing and facilitated the effects of 'paw pinch' in the current-evoked activity. Four of the nine cells recoded exhibited non-bistable membrane potentials, whereas 5/9 cells exhibited bistability. Separating the cells between bistable and non-bistable yielded no difference in the trend of the results (bistable cells baseline: 5.8 ± 1.9 spikes/pulse; SCH 23390: 2.9 ± 1.2 spikes/ pulse. paw pinch 8.6 ± 1.3 spikes/pulse n=5; non-bistable cells baseline: 4.3 ± 0.5 spikes/pulse; SCH 23390: 3.6 ± 0.9 spikes/pulse; paw pinch: 8.9 ± 2.6 spikes/pulse, n=4).

Effects of 'paw pinch' on spontaneous firing of PFC neurons

The effects of 'paw pinch' on spontaneous firing were also assessed in the recordings. However, 11 of the 18 cells recorded were silent during baseline recordings; therefore those cells were not included in the analysis of spontaneous firing. In the remaining seven cells, 'paw pinch' elicited a significant and transient decrease in the spontaneous activity of PFC cells (baseline: 3.2 ± 0.8 Hz; paw pinch: 1.9 ± 0.5 Hz, paired t-test $p < 0.01$, n=7, Fig. 2A). Systemic administration of sulpiride (15 mg/kg) prevented the decrease in spontaneous firing frequency previously elicited by 'paw pinch' (baseline: 3.2 ± 0.8 Hz; sulpiride: 5.1 ± 1.6 Hz; paw pinch: 3.9 ± 1.7 Hz, n=9 Fig 2B) suggesting that D2 receptors are active in

modulating cortical encoding of somatic signals. Finally, systemic administration of SCH 23390 (1.0 mg/Kg) significantly decreased spontaneous activity while also preventing the effects of 'paw pinch'(baseline: 3.1 ± 1.1 Hz, SCH 23390: 0.82 ± 0.2 Hz, paw pinch:10.4 ± 3.1 Hz n=3, ANOVA $F[2,46]= 20.2$ $p< 0.001$; Fisher post-hoc test $p< 0.001$, Fig 2C).

Collectively, these data suggest that modulation of PFC neuronal firing following strong somatic stimuli is dependent on dopaminergic receptors.

Discussion

The results of the present study show that strong somatic stimulation can induce: A decrease in the spontaneous activity of PFC neurons accompanied by an increase in current-evoked excitability, primarily in cells that do not exhibit membrane bistability. Administration of the selective DAergic D2 receptor antagonist sulpiride prevented the effects of somatic stimuli, suggesting that D2 receptors play an important role in the cortical encoding of strong somatic stimuli under anesthetized conditions. In contrast, administration of a selective D1 antagonist *facilitated* the effects of somatic stimuli in current-evoked firing.

Effects of membrane bistability

Our results show that somatic stimuli principally affected pyramidal cells not exhibiting membrane bistability. Previous reports, using *in vivo* intracellular recordings in the PFC, have shown that nearly 50% of pyramidal cells exhibit membrane bistability in anesthetized recording conditions (Lewis and O'Donnell, 2000; Trantham et al., 2002). Membrane bistability has also been observed: during natural sleep, under certain forms of anesthesia (Metherate and Ashe, 1993; Steriade et al., 1993; Cowan and Wilson, 1994; Timofeev et al., 2000) and – in some cases – in freely-moving animals (Petersen et al., 2003). The results presented demonstrate a correlation between the effects of 'paw pinch' and firing frequency for current-evoked activity.

Our results also show that for current-evoked activity, there is a correlation between the effects of paw pinch and firing frequency. Consequently, cells with lower firing frequencies exhibited the largest increases following application of paw pinch. A possible functional advantage of just such a mechanism might be that the large variability in PFC neuronal firing rates would become immediately normalized following an event of behavioral significance or salience. This would re-establish a baseline response across the entire network of the PFC, clearing the active encoding of recent information, thus allowing new information unfettered access to the putative working-memory buffers within the PFC. Moreover, it suggests that the state of the neuron plays a critical role in the encoding of strong somatic stimuli.

Differential effects of 'paw pinch' in spontaneous firing and current-evoked firing

These results show that somatic stimulation increases the current-evoked firing of cortical cells while decreasing their spontaneous firing. The mechanisms underlying spontaneous firing and evoked firing *in vivo* are different. Spontaneous firing of pyramidal neurons *in vivo* presumably arises from spontaneous synaptic inputs and their interplay with intrinsic conductances, as these neurons do not display intrinsic peacemaking ability. Conversely, the response to somatic current injection is more strongly mediated by intrinsic conductances. Perhaps spontaneous firing in the network represents the basal "noise" in the system, whereas current-evoked firing (mimicking synchronous depolarizing inputs impinging onto a cell) represents the "signal". The response to the signal would be influenced by spontaneous simultaneous activity, highlighting the functional importance of the "noise". Given these results, we propose that the overall effect of physically salient sensory stimuli is

to decrease background activity while heightening the response to salient inputs, particularly in neurons that are firing at low rates. This is supported by our results demonstrating that strong somatic stimulation produces both a reduction in spontaneous firing and a prolonged increase in current-evoked firing

Effects of dopaminergic antagonists on the increase in current-evoked excitability mediated by activation of somatic stimuli

We have previously established that the activation of both, D1 and D2 receptors are required for the expression of the VTA-induced increase in current-evoked excitability in the PFC (Lavin et al., 2005). The present results indicate that DA receptors modulate the effects induced by the application of strong somatic stimuli under anesthetic conditions. It is important to note that the DAergic antagonists were injected peripherally and affected widespread DA terminal fields, therefore is not possible to ascertain that the effects were mediated directly in the PFC.

Although the levels of DA in PFC increased following aversive stimuli, the firing of DAergic neurons in the VTA is usually reduced by such stimuli and it is only the non-dopaminergic VTA cells that show an increase in activity (Ungless et al, 2004). Likewise, DA neuronal firing is reduced transiently by negative reinforcement or the omission of an expected reward (Schultz, 1998; Ungless et al., 2004). Therefore aversive stimuli do not affect the firing of midbrain DA neurons, even though such stimuli cause DA release in the PFC. As we have shown in the present study, strong somatic stimulation can modulate PFC activity via activation of DAergic receptors. Of course, a limitation of our study is that is not possible to directly compare a strong somatic stimulation in an anesthetized animal with aversive stimuli in a conscious animal. Moreover, it is important to indicate that our conclusions are based in limited numbers of cells and single dose injections of DAergic drugs.

In summary, our results indicate that strong somatic stimuli modulate spontaneous and current-evoked activity in a different and opposite manner, decreasing spontaneous activity while increasing current-evoked activity, especially in low activity regimes. More importantly, we demonstrate that the effects of aversive stimuli on cortical firing are modulated by DAergic receptors. Remarkably, both VTA stimulation and aversive stimuli have the same net-effect by differentially modulating both evoked and spontaneous firing. Therefore, a salient event – regardless of its valence – may normalize activity across the PFC, hence enhancing its signal to noise properties for sometime thereafter.

Experimental procedures

Animal preparation

All animals were handled in accordance with the procedures outlined in the *Guide for the Care and Use of Laboratory Animals* published by the US Public Health Service, and the Medical University of South Carolina Animal Care and Use Committees approved the specific protocol. Subjects were male Sprague Dawley rats (Charles River Laboratories, Wilmington, MA), weighing 200–250 g at the start of the experiment. Animals were housed in pairs in a temperature-controlled colony room on a 12 h light/dark cycle (lights on at 7:00 A.M.), and food and water were available *ad libitum*. Animals were allowed to acclimatize to the colony room for 3–5 d after their arrival.

Intracellular recordings in vivo

Rats were anesthetized with a mixture of ketamine/xylazine (70 and 5 mg/kg, i.p., respectively) and placed in a stereotaxic apparatus. The temperature of the animal was

maintained at 36 ± 0.5°C through a thermostatically controlled heating pad. The levels of anesthesia were maintained constant by the use an ip cannula connected to a peristaltic pump infusing the mix of anesthetics at 0.5 μl/min. The cisterna magna was drained, and a hole was drilled over the PFC [coordinates from bregma: anteroposterior (AP), 3.2 mm; lateral (L),± 0.6 mm; ventral (V), 4 –5.0mm at 10° inclination] (Paxinos and Watson, 1998). Int racellular microelectrodes were pulled from Omegadot tubing (outer diameter, 1.5 mm; World Precision Instruments, Sarasota, FL). The electrodes were filled with 3 M potassium acetate (electrode resistance, 25–40 MΩ *in situ*). Impalements were defined as stable if the resting membrane potential was more negative than −55 mV and the action potential amplitude was at least 50 mV. A headstage amplifier connected to a preamplifier (NEURODATA IR-283; Cygnus Technology, Delaware Water Gap, PA) amplified signals.

Current was injected across a bridge circuit, with electrode potentials and current injection amplitude monitored on a personal computer screen using a National Instruments (Austin, TX) A/D board as an interface to a computer running custom Labview software. After successful impalement of a cell, 10 min of stable baseline recordings were obtained before experimental recordings began. The spontaneous activity of the cells was recorded in bins of 10 s, every 30 s throughout the experiment. The current-evoked excitability was recorded in bins of 1 s every 30 s throughout the experiment by passing a constant-current pulse (1 s duration) that evoked at least three action potentials during baseline recordings. That current pulse was maintained throughout the rest of the experiment. Immediately following paw pinch, data were collected for spontaneous activity (30 sec) followed by current-evoked pulses (1 sec). Through all of the experiments, the membrane potential was monitored closely, and small changes in *V*m were corrected by addition of current via the recording electrode. In an effort to deliver a constant somatic stimuli across all the animals tested, metal forceps were used to apply pressure (10 sec) across a patch of skin located between the phalanx of the first and fifth toe of the posterior right limb. The metal forceps were always locked in the first position for all the rats, so delivering always the same pressure. Henceforth, this mechanical pressure will be termed the somatic stimulus.

Drugs were administered intraperitoneally (sulpiride, 15 mg/kg; Vives and Mogenson, 1986; Yanagihashi et al., 1991; Rosa-Kenig et al., 1993; SCH 23390 [*R*(_)-7-chloro-8-hydroxy- 3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3- benzazepine hydrochloride], 1.0 mg/kg; Lewis and O'Donnell, 2000; Brady and O'Donnell, 2004; Daniela et al., 2004)].

Histology and statistics

At the end of the experiments, the animals were given an overdose of anesthetic and perfused transcardially with saline, followed by 10% buffered formalin. The brain was removed and placed in a solution of 15% sucrose at 4°C. Coronal slices 60 μm thick, were cut using a freezing microtome and collected in phosphate buffer. The slices were stained with cresyl violet to aid in the localization of the electrode track and the stimulating electrode. The spontaneous and current-evoked firing of neurons recorded in the PFC was compared using a paired two-tailed, two-sample Student's *t* test or ANOVA test with repeated measures and *post hoc* Fisher's test. Statistical significance was set at $p<0.05$ and all results are presented as mean± SEM.

Research Highlights

- Somatic stimulation (paw pinch) decreases prefrontal cortical spontaneous firing
- Somatic stimulation (paw pinch) increases prefrontal cortical depolarization-evoked firing

- Systemic administration of DAD2 antagonists partially blocks the effects of somatic stimulation in PFC.
- Systemic administration of D1 antagonists seem to facilitate paw-pinch mediated increases in evoked firing

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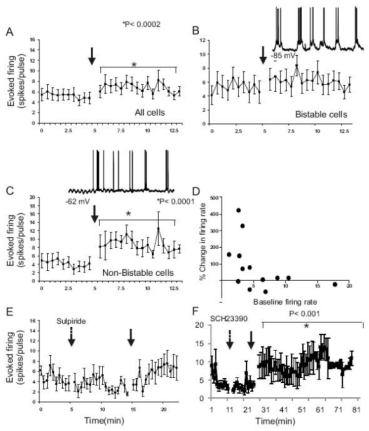

Figure 1.

Delivery of aversive stimuli (paw pinch) elicited changes in current-evoked activity on pyramidal cells of the prefrontal cortex. A) Aversive stimuli (paw pinch for 10 sec) elicited a significant increase (paired t-test $p< 0.0002$) in current-evoked activity recorded in pyramidal cells (n=18), B) When cortical cell activity was divided between neurons that exhibit bistable and non-bistable membrane, it was found that paw pinch had no effect on the current-evoked activity of bistable neurons, C) In contrast, paw pinch elicited a significant increase (paired t-test $p< 0.0001$) in the current evoked activity of non-bistable cells. D) The increase in current-evoked activity elicited by paw pinch was inversely correlated with the basal firing rate (correlation coefficient= 0.46), E) systemic administration of the D2 antagonist sulpiride (15 mg/kg ip) blocks the increase in current-evoked excitability elicited by paw pinch, F) Systemic administration of the D1 antagonist SCH (1.0 mg/kg ip) failed to block the increase in current-evoked excitability elicited by the paw pinch (ANOVA $F[92,18]=27.9$ $p<0.001$ Fisher post-hoc test $p<0.001$). The fill arrows indicate the time of application of noxious stimuli. The dotted arrows indicate the administration of DAergic antagonist.

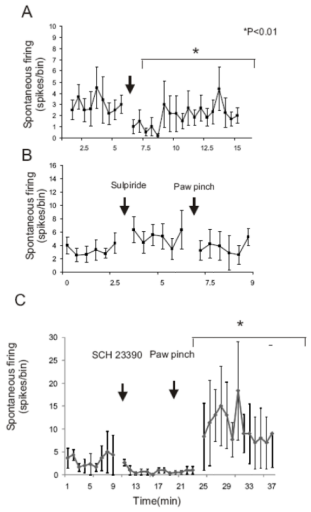

Figure 2.

Effects of aversive stimuli in the spontaneous excitability of PFC neurons. A) Paw pinch decreased spontaneous cortical activity (paired t-test $p<0.01$), B) Systemic administration of the D2 antagonist sulpiride (15 mg/kg ip) prevented the changes in spontaneous activity elicited by paw pinch. C) Systemic administration of the D1 antagonist SCH 23390 (1.0 mg/kg ip) decreases spontaneous firing rate and facilitates the effect of somatic stimulation.