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Dendritic glutamate-induced bursting in prefrontal pyramidal cells: role of NMDA and non-NMDA receptors[1]

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KEY WORDS electrophysiology; *N*-methyl-*D*-aspartate receptors; sodium glutamate; dendrites; prefrontal cortex; pyramidal cells; action potentials; iontophoresis

ABSTRACT

AIM: To investigate whether in the prefrontal cortical (PFC) pyramidal cells, focal glutamate application to the apical dendrite induces bursting and whether the effect of glutamate involves activation of both NMDA and non-NMDA receptors. **METHODS**: Pyramidal cells in layers V and VI of the PFC were visualized in rat brain slices using infrared videomicroscopy and recorded with whole-cell electrodes. Glutamate and its agonists were focally applied to the apical dendrite and the soma using microiontophoresis. **RESULTS**: Dendritic glutamate application (0 - 20 nA, 10 mmol/L) induced repetitive bursts in most cells tested (12/17). In the same cells, somatic glutamate (5 - 20 nA, 10 mmol/L) induced only regular spiking. The bursting effect is likely to be direct since applications 5 μm away from the dendrite resulted in either a much reduced effect or no effect. Both CGP 37849 1 μmol/L and NBQX 1 μmol/L reduced the effect, suggesting an involvement of both NMDA and non-NMDA receptors. However, when non-NMDA receptors were selectively activated using AMPA (2 - 50 nA, 10 mmol/L), only regular spiking was observed. In contrast, selective NMDA receptor activation (NMDA 1.3 - 25 nA, 100 mmol/L) reliably induced bursting. **CONCLUSION**: In most PFC pyramidal cells tested, dendritic glutamate application induces repetitive bursting, whereas somatic glutamate application induces only regular spiking. Both NMDA and non-NMDA receptors are activated during dendritic glutamate application. However, bursting is primarily mediated by NMDA receptors.

INTRODUCTION

Cortical neurons are classified as either pyramidal or non-pyramidal cells[1]. The main feature that distinguishes a pyramidal cell from a non-pyramidal cell is the presence of the apical dendrite in the former. Based on the electrophysiological characteristics, pyramidal neurons can be further divided into regular spiking and intrinsic bursting cells[2-4]. The latter differ from regular spiking cells in that they are capable of firing in bursts in response to membrane depolarization produced by intracellular current injection. In contrast, regular spiking cells fire only repetitive single spikes. In some regular spiking cells, a depolarization step may evoke a single initial burst followed by regular spiking. Based on this classification, most cortical pyramidal cells belong to regular spiking cells. This traditional classification, however, has recently been challenged by Schwindt *et al*[5]. In their studies in the sensorimotor cortex, nearly all cells identified as regular-spiking cells were able to fire repetitive bursts when the apical dendrite was depolarized by focal glutamate application. In the same population of cells, somatic glutamate application, like intrasomatic current injection through the recording electrode, evoked only regular spiking. These results suggest that both intrinsic bursting cells and regular spiking cells are

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capable of bursting repetitively upon depolarization. In regular spiking cells, however, repetitive bursting is induced by dendritic depolarization and not by somatic depolarization. These findings support the suggestion that the location of a synaptic input determines not only the amplitude (quantity) but also the dynamics (quality) of the response of the cell to the input. These findings also emphasize the role of the apical dendrite in the bursting activity observed in regular spiking cells.

The present study was designed to test first whether pyramidal cells in the prefrontal cortex (PFC) also show different responses to glutamate applied to the soma and the apical dendrite. The PFC, an important target area for dopamine, serotonin, and norepinephrine neurons, has been suggested to play a critical role in behaviors associated with cognition, motivation, and emotion[6-11]. Evidence suggests that PFC glutamate-mediated neurotransmission may be altered in disorders such as schizophrenia and drug addiction[12-17]. A better understanding of glutamate transmission in the PFC may, therefore, provide new insights into the pathophysiology of these disorders. Different from studies by Schwindt *et al*[5], the present study was carried out on visualized cells using infrared video-microscopy. With this technique and by applying glutamate more precisely to the apical dendrite of a recorded cell, the present study examined further whether the response induced by dendritic glutamate involves activation of glutamate receptors on adjacent cells near the application site. More importantly, using subtype selective agonists and antagonists, the present study asked whether both NMDA and non-NMDA receptors play a role in dendritic glutamate-induced bursting.

MATERIALS AND METHODS

Preparation of slices All procedures were performed in accordance with those outlined in the Guide for the Care and Use of Laboratory Animals published by the USPHS and approved by the Yale Animal Care and Use Committee. Male Sprague-Dawley albino rats weighing between 50 to 75 g (Charles River Laboratories, Wilmington MA) were used. Brain slices were prepared as described previously[18,19]. Briefly, rats were anesthetized with chloral hydrate (400 mg/kg, ip) and decapitated. The brains were quickly dissected and submerged in an ice-cold medium containing (in mmol/L) NaCl 125, KCl 3, $MgSO_4$ 1.4, $CaCl_2$ 1.2, NaH_2PO_4 1.2, $NaHCO_3$ 25, glucose 10, sucrose 10, and saturated with 95 % O_2 + 5 % CO_2. A block of tissue containing the PFC was cut and glued on the cutting stage of a vibratome (OTS-4000 tissue slicer, FHC Inc, Bowdoinham, ME). Serial coronal slices (280 – 300 μm) were cut and transferred to an incubating chamber where they were held at 35 ℃ for at least 1 h before recording.

Electrophysiological recording During recording, slices were continuously perfused at room temperature in a chamber placed on the fixed stage of an upright microscope equipped with an infrared sensitive CCD camera (CCD-300T-RC, Dage-MTI, Michigan City, IN). Individual cells were visualized using Nomarski optics and a 40 × long working distance, water immersion objective (3.3 mm, NA: 0.8, Olympus, Japan). Recording electrodes were pulled from thin-walled glass capillaries (OD = 1.5 mm, WPI, Sarasota, FL), filled with a solution containing (in mmol/L) Kgluconate 140, $CaCl_2$ 0.1, $MgSO_4$ 2, egtazic acid 1, $ATPK_2$ 2, $GTPNa_3$ 0.1, HEPES 10, and 0.5 % biocytin pH 7.25, and had a resistance of 7 – 12 MΩ. Voltage and current signals were recorded with an Axoclamp-2A (Digidata 1200, Axon, Foster City, CA) interfaced to a personal computer (Dimension XPS Pro200n, Dell, Austin, TX). Data were digitized and stored on disks using jClamp (v.3.4, J Santos-Sacchi, Yale University). Off-line data analysis was performed using pClamp, Systat (Systat Inc, Evanston, IL) and Visual Basic Macros in Microsoft Excel.

Drug application Drugs used in this study were NMDA (*N*-methyl-*D*-aspartate, Research Biochemicals International, Natick, MA), AMPA [*d*,*l*-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, RBI], NBQX (1,2,3,4-tetrahydro-6-nitro-2,3-dioxo-benzo[f]quinoxaline-7-sulfonamide, RBI), CGP37849 (Ciba-Geigy, Basel, Switzerland)

Glutamate and its agonists were applied focally through a 3-barrel microiontophoretic electrode (overall tip diameter 2 – 3 μm). One barrel was filled with NaCl 0.5 mol/L and used as the balance electrode. Through the balance electrode, a current was constantly

and automatically adjusted so that the sum of the current through all 3 barrels equaled zero. The use of a balance electrode allowed to reduce current artifact and to minimize diffusion of drugs away from the application site. The remaining two barrels were filled with either glutamate (10 mmol/L, pH 8.5), NMDA (100 mmol/L, pH 8.5) or AMPA (10 mmol/L, pH 8.5). A positive retaining current (10 nA) was used to eliminate the passive diffusion while the drug was not ejected. All drugs were ejected with negative currents ranging from 0 – 50 nA. Glutamate antagonists were administrated through the bath.

Biocytin staining At the end of recording, slices were fixed overnight with 4 % paraformaldehyde in phosphate buffer saline (PBS, pH 7.4) and transferred to PBS containing 0.5 % Triton X-100 and 1 % hydrogen peroxide for 3 h. Slices were then washed with PBS, incubated with avidin-biotinylated peroxidase-complex (Vectstain Elite ABC kits PK-6100, Vector Laboratories Inc, Burlingame, CA) in the presence of 0.5 % Triton X-100 for 36 h, and reacted with diaminobenzidine and hydrogen peroxide.

RESULTS

All cells reported in this study (n = 29) were inactive with resting potentials ranging from – 59 mV to – 67 mV (without the correction of the junction potential between the electrode and the bath). All cells, however, were capable of firing repetitively in response to intrasomatic depolarization current injection (20 – 160 pA for 3.5 s). Most cells (28/29) showed an initial burst of 2 – 3 spikes followed by regular spiking (Fig 1). In one cell, only regular spiking was observed. None of the cells tested showed repetitive bursts.

Repetitive bursting induced by dendritic glutamate application Unlike intrasomatic current

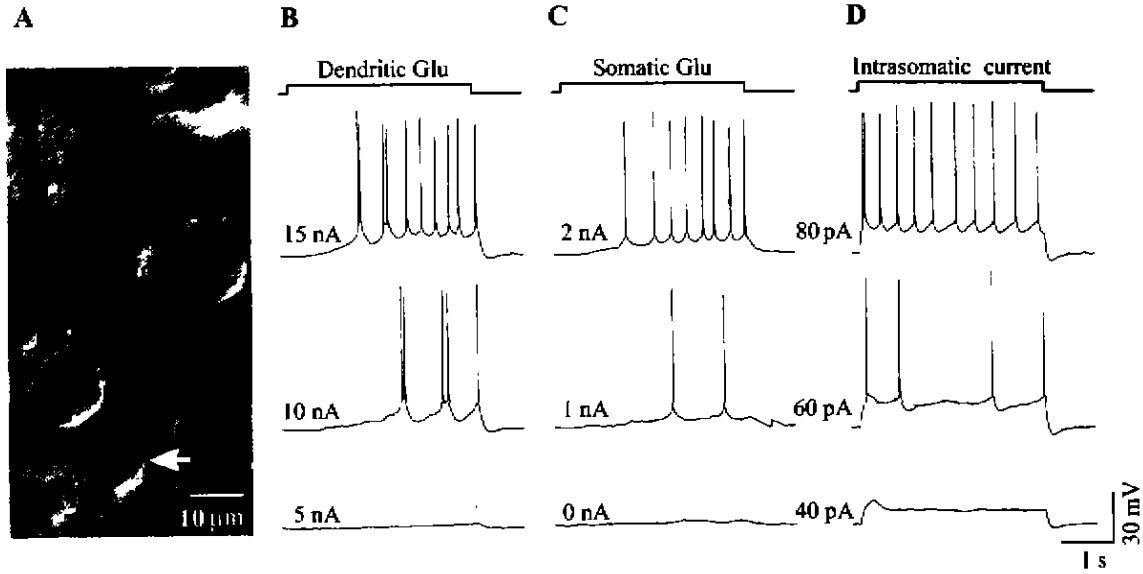

Fig 1. Different firing patterns induced by glutamate applied to the soma and the apical dendrite. A) Infrared image of live cells in layers V – VI of a PFC slice. The cell shown in the middle was being recorded with a whole-cell electrode at the soma. On the apical dendrite of the recorded cell was a microiontophoretic electrode containing glutamate. The same microiontophretic electrode was latter moved to the soma (white arrow). Responses of the cell to glutamate (Glu) are shown in B and C. B) Whole cell recordings showing burst firing induced by dendritic glutamate application. Note the two doublets and the underlying large membrane oscillation evoked by both 10 and 15 nA of glutamate (10 mmol·L^{-1}, pH 8.5). At 15 nA of glutamate, the doublets were followed by regular spiking. C) Responses of the same cell to somatic glutamate application. Although the cell was depolarized to similar levels as in B, only regular spiking (repetitive single spikes) was evoked; no doublet or large membrane oscillation was observed. D) Intrasomatic current injection through the recording electrode evoked either regular spiking or a single doublet followed by regular spiking; no repetitive bursting was observed.

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E-mail aps@server shcnc.ac.cn Phn/Fax 86-21-6474-2629

injection, focal glutamate application (0 – 20 nA for 3.5 s) to the apical dendrite (50 – 100 μm away from the soma) induced repetitive bursting in most cells tested (12/17, Fig 1). In the remaining 5 cells, dendritic application of glutamate induced only regular firing. The number of bursts evoked varied between 2 to 5 depending on the cell examined and the amount of glutamate applied. At low glutamate ejection currents, the number of bursts increased with increasing glutamate currents. At high glutamate currents, however, a further increase in glutamate currents often led to a decrease in bursting accompanied by an increase in regular spiking.

In 9 cells where dendritic glutamate induced repetitive bursts, the microiontophoretic electrode was moved to the soma. In all 9 cells, somatic glutamate application (5 – 20 nA for 3.5 s) induced only regular spiking (Fig 1).

To be sure that somatic glutamate receptors do not contribute significantly to dendritic glutamate-induced bursting, and to test whether dendritic glutamate-induced bursting involves activation of neighboring neurons located near the application site, glutamate was applied to sites about 5 μm away from the dendrite. As shown in Fig 2, at both sites 1 and 4 on the apical dendrite, glutamate reliably produced bursting. However, when the application electrode was moved to sites 2 and 3 (both about 5 μm away from the dendrite but closer to the soma compared with site 4), the same amount of glutamate evoked only a small depolarization; no bursting or firing was observed. Similar experiments were performed in 3 other cells and identical results were obtained.

Role of NMDA and non-NMDA receptors in glutamate-induced bursting To determine whether glutamate acts through both NMDA and non-NMDA receptors to induce bursting, the selective NMDA antagonist CGP37849 and the non-NMDA antagonist NBQX (both at 1 μmol/L) were applied through the bath. In all 3 cells tested, dendritic glutamate-induced bursting were reversibly blocked by CGP37849 and NBQX. In the presence of either antagonist, glutamate produced only a subthreshold depolarization (Fig 3). When CGP37849 and NBQX were co-administered, the effect of glutamate was completely blocked.

In 11 cells, NMDA and AMPA were applied to

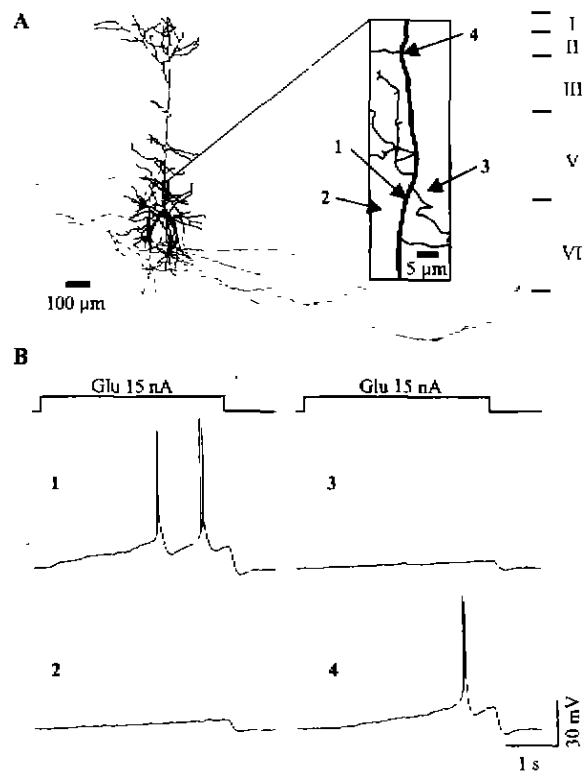

Fig 2. Comparison of the responses induced by glutamate applied to different sites on and near the dendrite. A) Reconstruction, based on intracellular biocytin staining, of a pyramidal cell in layer VI. Glutamate (Glu, 10 mmol/L, pH 8.5) was applied to 4 sites labeled as sites 1, 2, 3, and 4, respectively (inset). B) Whole cell recordings shown responses of the cell to glutamate applied at the 4 different sites. At site 1, glutamate (15 nA) reliably evoked two doublets. At sites 2 and 3 (both about 5 μm away from the dendrite), the same amount of glutamate induced only a small depolarization. Site 4 is further away from the soma but directly on the dendrite. Application of glutamate to this site induced a triplet.

selectively activate NMDA and non-NMDA receptors, respectively. In all cells, dendritic NMDA (1.3 to 25 nA) reliably induced repetitive bursting, whereas AMPA, applied through the same multibarrel electrodes (2 – 50 nA), induced only regular spiking (Fig 4A). The bursting effect of NMDA was unaffected by NBQX (5 μmol/L, $n = 6$) and completely inhibited by CGP37849 (1 μmol/L). The regular spiking induced by AMPA, on the other hand, was selectively blocked by NBQX (1 μmol/L) not affected by CGP37849 (5 μmol/L, $n = 3$) (Fig 4B).

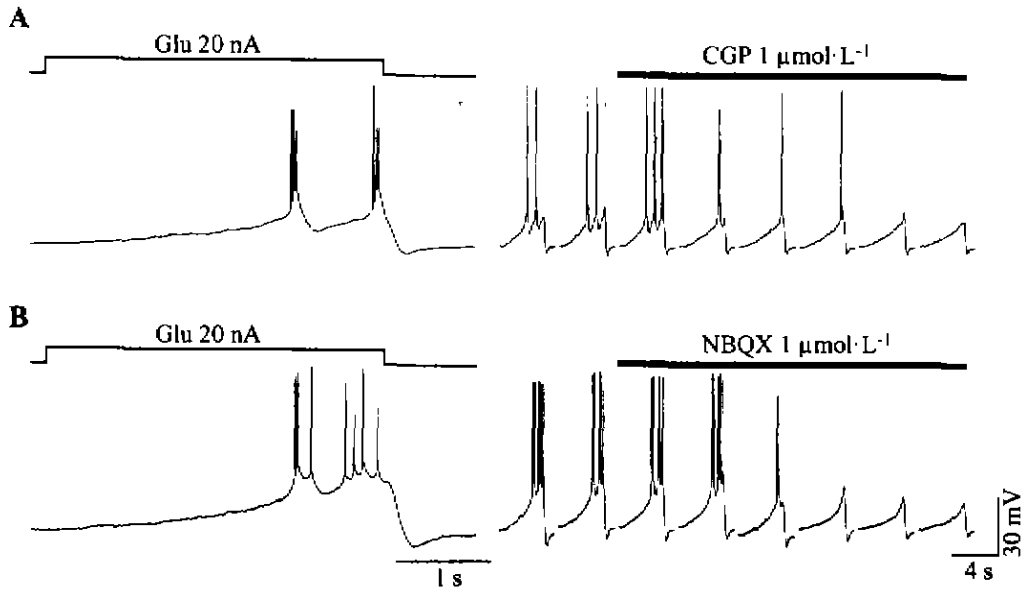

Fig 3. Blockade of glutamate-induced bursting by both NMDA antagonist and non-NMDA antagonist. A) Whole cell recordings from a PFC pyramidal cell showing glutamate-induced bursting and its blockade by the NMDA antagonist CGP37849 (CGP). B) Recordings from a different cell showing the blockade of glutamate-induced bursting by the non-NMDA antagonist NBQX. In both cells, glutamate (10 mmol·L^{-1}, pH 8.5) was applied every minute for 3.5 s. Note that the first recording in both cells was shown on an expanded time scale.

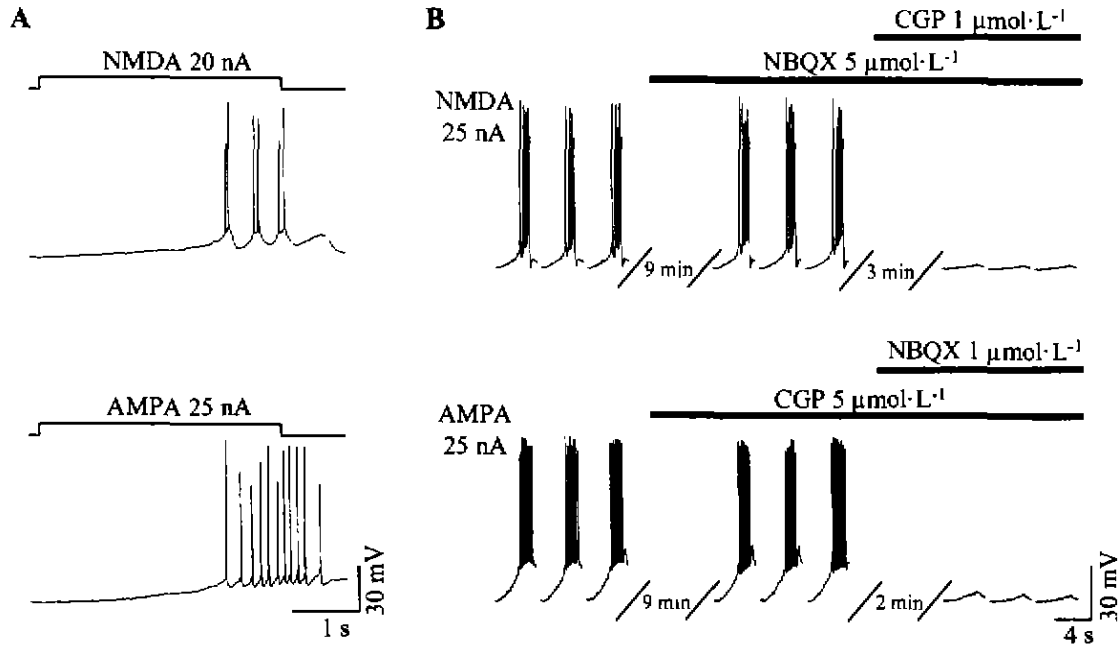

Fig 4. Bursting and regular spiking induced by selective activation of NMDA and non-NMDA receptors, respectively. A) In this pyramidal cell, NMDA and AMPA were applied through the same multibarrel microiontophoretic electrode to the apical dendrite. NMDA (100 mmol·L^{-1}, pH 8.5) reliably induced bursting, whereas AMPA (10 mmol·L^{-1}, pH 8.5) evoked only regular spiking. B) In a different cell, NMDA-induced bursting was unaffected by the non-NMDA antagonist NBQX and blocked by the NMDA antagonist CGP37849 (CGP). In another cell, the regular firing induced by AMPA persisted in the presence of CGP37849 and was largely blocked by NBQX. In both cells, NMDA or AMPA was applied every 30 s for 3.5 s.

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DISCUSSION

The first major finding of the present study is that in the PFC, focal glutamate application to the apical dendrite induces repetitive bursts. In the same cells, somatic glutamate application, like intrasomatic current injection, induces only regular spiking. These observations are consistent with those previously reported in the sensorimotor cortex[5]. However, in the latter area, bursting was observed only when glutamate was applied to more distal dendrites (> 200 μm from the soma). In the present study, applications at proximal locations (50 – 100 μm from the soma) also reliably evoked bursting. The cause for the differences is unclear. It is possible that neurons in the PFC are different from those in the sensorimotor cortex. However, in previous studies using a regular slice preparation, the iontophoretic electrode was only roughly positioned; how far it was from the apical dendrite of a recorded cell was not precisely determined. Thus, it may be possible that in those studies, the amount of glutamate applied may have also activated somatic glutamate receptors, thereby leading to regular spiking. In the present study, experiments were performed on visualized cells. The microiontophoretic electrode was placed precisely on the dendrite of a recorded cell. Because of this close proximity, the amount of glutamate needed to evoke a dendrite-mediated response should be reduced to the minimum and so the diffusion of glutamate to the soma. The use of a balance electrode may further limit glutamate diffusion from the ejection site. Indeed, when applied just a few micrometers away from the dendrite but closer to the soma, the same amount of glutamate, previously shown to cause bursting at the dendrite, now induced only a small depolarization.

The second major finding of the present study is that NMDA and non-NMDA receptors play different roles in glutamate-induced bursting. We showed that both NMDA and non-NMDA antagonists attenuated glutamate-induced depolarization and blocked the bursting. However, when agonists were used to selectively activate NMDA and non-NMDA receptors, respectively, only NMDA receptor activation caused bursting. Activation of non-NMDA receptors, on the other hand, induced only regular firing. These results suggest that dendritic glutamate-induced bursting is primarily mediated through NMDA receptors. However, concurrent activation of non-NMDA receptors may, by depolarizing the cell, enhance NMDA receptor-mediated bursting.

The lack of an ability of AMPA to induce bursting also raises the question whether a simple dendritic depolarization is enough to cause bursting. In hippocampal CA1 pyramidal cells, a depolarizing current injection through an intradendritic electrode was reported to evoke burst-like firing[20]. However, only short pulses of current were tested and the cell fired only a single burst. Thus, whether or not a more prolonged intradendritic depolarization can induce repetitive bursts remains uncertain. Our results with NMDA suggest that repetitive bursting may require both membrane depolarization and an entrance of Ca^{2+} into the dendrite.

Why then is somatic glutamate ineffective in inducing bursting? There are several possible answers to this question. For example, NMDA receptors on the soma may not be as dense as on the dendrite, or there are more AMPA receptors on the soma than on the dendrite. It is also possible that other mechanisms (*eg*, certain ionic channels) are also needed for the generation of bursting and that these mechanisms are absent in the soma. Clearly, more studies are needed to test these and other possibilities.

The finding that activation of NMDA receptors induces bursting may have important implications for understanding the function of NMDA receptors in the PFC and related disorders. It is well known that noncompetitive NMDA antagonists such as phencyclidine (PCP) can induce symptoms almost indistinguishable from schizophrenia[21]. Part of the psychotogenic effect is believed to be mediated by blockade of NMDA receptors in the PFC[22]. However, how this blockade eventually leads to the development of psychotic symptoms remains largely unclear. Both dopamine and glutamate levels in the PFC are increased following the treatment with a PCP-like antagonist[22,23], suggesting that both dopamine and glutamate may play a role. The present study suggests that an NMDA antagonist also alters firing patterns of PFC pyramidal cells. Such alteration may also contribute to the psychotogenic effect induced by an NMDA antagonist.

In conclusion, the present study shows that in most PFC pyramidal cells, glutamate application to the

apical dendrite induces repetitive bursts. In the same cells, somatic glutamate application or intrasomatic depolarization current injection induces only regular spiking. Our data further suggest that the burst firing induced by dendritic glutamate is primarily mediated by activation of NMDA receptors.

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谷氨酸树突处局部给药所引起的前额皮层锥体细胞爆发式放电：NMDA 和非 NMDA 受体的作用

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关键词 电生理学；*N*-甲基-*D*-天冬氨酸；谷氨酸钠；树突；额页前部皮质；锥体细胞；动作电位；离子透入法 (责任编辑 李 颖)