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AUDITORY INHIBITORY GATING IN MEDIAL PREFRONTAL CORTEX: SINGLE UNIT AND LOCAL FIELD POTENTIAL ANALYSIS

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Abstract—Medial prefrontal cortex is a crucial region involved in inhibitory processes. Damage to the medial prefrontal cortex can lead to loss of normal inhibitory control over motor, sensory, emotional and cognitive functions. The goal of the present study was to examine the basic properties of inhibitory gating in this brain region in rats. Inhibitory gating has recently been proposed as a neurophysiological assay for sensory filters in higher brain regions that potentially enable or disable information throughput. This perspective has important clinical relevance due to the findings that gating is dramatically impaired in individuals with emotional and cognitive impairments (i.e. schizophrenia). We used the standard inhibitory gating two-tone paradigm with a 500 ms interval between tones and a 10 s interval between tone pairs. We recorded both single unit and local field potentials from chronic microwire arrays implanted in the medial prefrontal cortex. We investigated short-term (within session) and long-term (between session) variability of auditory gating and additionally examined how altering the interval between the tones influenced the potency of the inhibition. The local field potentials displayed greater variability with a reduction in the amplitudes of the tone responses over both the short and long-term time windows. The decrease across sessions was most intense for the second tone response (test tone) leading to a more robust gating (lower T/C ratio). Surprisingly, single unit responses of different varieties retained similar levels of auditory responsiveness and inhibition in both the short and long-term analysis. Neural inhibition decreased monotonically related to the increase in intertone interval. This change in gating was most consistent in the local field potentials. Subsets of single unit responses did not show the lack of inhibition even for the longer intertone intervals tested (4 s interval). These findings support the idea that the medial prefrontal cortex is an important site where early inhibitory functions reside and potentially mediate psychological processes. © 2006 IBRO. Published by Elsevier Ltd. All rights reserved.

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Neural inhibition and prefrontal cortex (PFC) have been linked in numerous studies examining diverse groups from patient populations to a variety of mammalian animal models (Swerdlow et el., 2005; Egner and Hirsch, 2005; Shoemaker et al., 2005; Likhtik et al., 2005; Knight et al., 1999). Evidence that the PFC is important for neural inhibition is very well supported yet the functional significance of the intrinsic or extrinsic PFC inhibitory control remains mostly unknown. Relevant work on the functional role has investigated patients or animals with PFC damage and found that this region is important for short-term attention to external stimuli (Carli et al., 2006; Bailey and Mair, 2004; Knight et al., 1995). In human patients with focal lesions to the PFC or animals with experimental PFC damage inhibitory control of sensory processing is significantly impaired (Knight et al., 1989; Yamaguchi and Knight, 1990, 1991; Rosenkranz and Grace, 2001). These same populations have severe problems in attending to relevant versus irrelevant stimuli (Woods and Knight, 1986; Christakou et al., 2001). PFC dysfunction leads to defective identification of novel stimuli (Knight, 1984) and causes a loss of inhibitory control over internal processes involved in integrating cognition and emotion (Rule et al., 2002; Phan et al., 2005; Maren and Quirk, 2004; Runyan et al., 2004). Additionally, PFC damage can lead to a dramatic loss of behavioral inhibition that initiates a syndrome of impulsive behavior and maladaptive choice behavior (Carli et al., 2006; Chudasama et al., 2005).

Alterations to PFC function are thought to play a role in the etiology of schizophrenia (Cannon et al., 2005; Selemon, 2001; Weinberger et al., 2001). Schizophrenic patients similar to the patients with focal damage to the PFC have problems with attention and stimulus discrimination (Elliot et al., 1995; Pantelis et al., 1997, 1999). Moreover, a common symptom that schizophrenics express has been termed “sensory flooding” with a loss of input filtering that would normally “gate” incoming input from the various sensation sources (Venables, 1964, 1969). Other psychological disorders such as obsessive compulsive disorder, post-traumatic stress disorder and drug addiction have sensory filtering problems that could be described as “sensory flooding”(Rossi et al., 2005; Ghisolfi et al., 2004; Adler et al., 2001) and may all involve PFC dysregulation (Richert et al., 2006; van den Heuvel et al., 2005; Self, 1998). Each of these disorders has been examined using one particular index of inhibition, labeled P50 (positive wave at 50 ms) suppression or sensory inhibitory gating (IG). Several clinical groups are now using the paradigm as a way to gauge symptom progression and potentially diagnose certain psychological impairments (Louchart-de la Chapelle et al., 2005; Freedman et al., 1996).

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Abbreviations: A/D, analog-to-digital; cAmp, amplitude of response to C_{tone}; CTI, condition-test interval; C_{tone}, conditioning tone; ELD, excitatory long-duration; EP, evoked potential; ESD, excitatory short-duration; IG, inhibitory gating; Inh, inhibitory response; LFP, local field potential; mPFC, medial prefrontal cortex; PFC, prefrontal cortex; PPT, pedunculopontine nucleus; P50, positive wave at 50 ms; tAmp, amplitude of response to T_{tone}; T_{tone}, test tone; VTA, ventral tegmental area.

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Sensory IG is partially similar to other gating paradigms and differs in that it is not necessarily linked to a particular reflexive behavioral response. In this way, IG can be more of a pure index of sensory input gating rather than necessarily sensorimotor gating (Swerdlow et al., 2005). To measure IG in the clinical setting, the subject is placed in a quiet room and presented with pairs of sensory stimuli. In almost all the previous work, auditory stimuli have been used and the tone pairs are presented with a 500 ms intertone interval and a 10 s interval between tone pairs (Adler et al., 1998). Subjects are asked to relax but not to sleep and listen to the tones while evoked potentials (EPs) are recorded from the scalp. In normal subjects, a sharp reduction in the response to the second tone of the pair is observed (Waldo and Freedman, 1986). The second tone is labeled the test tone (T_{tone}) because it tests the integrity of the inhibitory network. The initial tone has been labeled the conditioning tone (C_{tone}) (see Freedman et al., 1996). In schizophrenic, PTSD, OCD patients and drug addicts the inhibition is reduced so that the responses appear much more similar in amplitude throughout the session period (Freedman et al., 1987; Adler et al., 2001; Rossi et al., 2005; Ghisolfi et al., 2004).

Using EPs to auditory stimuli, IG has been found in numerous locations throughout the CNS including brainstem, septum, hippocampus (Adler et al., 1986; Moxon et al., 1999; De Bruin et al., 2001) as well as primary auditory cortex (Moxon et al., 1999). EP recording has been the primary tool used to measure IG in both patients (Adler et al., 1982; Freedman et al., 1994; Boutros et al., 2004) and normal human and animal subjects (Boutros et al., 1995, 1997; Kisley et al., 2004). This technique pools information from a large number of neural elements. The P50 or positive wave at 50 ms following the stimulus has been the focal point of most investigations (Patterson et al., 2000; Olincey et al., 2000). Other potentials, including mid-latency potentials, have been shown to gate as well but not as robustly under certain conditions (Grunewald et al., 2003; Boutros and Belger, 1999).

Gating has been measured by single-unit tone responses in different brain regions such as the hippocampus (Bickford-Wimer et al., 1990; Miller and Freedman, 1995; Moxon et al., 1999), amygdala (Cromwell et al., 2005), and reticular nucleus of the thalamus (Krause et al., 2003). Interestingly, IG is weak to non-existent in a major relay in the lemniscal auditory pathway, the medial geniculate nucleus of the thalamus (Bickford-Wimer et al., 1990). The single unit analysis has provided a unique window into the basic properties of IG. For instance, IG is observed to different types of tone responses in the amygdala (Cromwell et al., 2005). These types of analyses of the precise details of IG suggest that it can be a pervasive and consistent mechanism in certain brain structures. These basic properties of IG using local brain region recording in freely moving animals have not been investigated in the PFC, a region thought to be crucial to IG.

Our primary goal with this research was to describe and examine the parametric qualities of IG in the medial prefrontal cortex (mPFC) using chronic recording wires to monitor both single unit and local field potential (LFP) responses simultaneously. By demonstrating and characterizing mPFC single-units, it was possible to establish IG as an inherent property of distinct subregions of the PFC. Another goal was to ascertain that IG was relatively stable over the course of multiple recording sessions and within the segments of a single recording session for LFPs and single-units. We hypothesized that both levels of neural activity would show a high degree of stability due to the fact that these tones were irrelevant and highly predictable. A final goal was to test IG for both LFPs and single-units at different intervals of separation between first and second tones in order to determine that an interval of optimal IG exists. We hypothesized that as the intervals increased, the strength of gating would decrease. These changes should be graded between the different delays and similar between the single unit and LFP level of activity within the mPFC.

EXPERIMENTAL PROCEDURES

Chronic microelectrode implantation

Animals were anesthetized with xylazine (10 mg/kg) and ketamine (100 mg/kg), and surgery was conducted according to procedures as described in protocols approved by nationally approved guidelines for the care and use of animals (USDA and PHS). All procedures were approved by the Bowling Green State University Animal Care and Use Committee. A stereotaxic apparatus was used for the implantation of recording microwires (NB Laboratories, Denison, TX, USA) into mPFC (A +2.7, M ±0.7, D −3.0) according to the standard rat stereotaxic atlas (Paxinos and Watson, 1998). Anchor screws were affixed to the skull surface to be used in the protective headstage. Rats were bilaterally implanted in mPFC with 16 microwires in two bundles of eight (one bundle in each hemisphere). Grounding wires were implanted bilaterally near bregma, but 3 mm lateral and 2–3 mm below dura. The recording electrodes were cemented into permanent placement using dental acrylic. After surgery, rats were allowed one week to recover before the beginning of testing.

Experimental apparatus

The testing chamber (20×28×35 cm) was located in a small sound attenuating room. The chamber floor had parallel rods that suspended the rat 5 cm above a removable pan. Piezoelectric tone generators were attached to the top of the chamber, and holes were drilled to allow sound to pass into the chamber. A tone generator produced a distinctive tone pitch of 4.1 kHz. A potentiometer on the tone generator was manually adjusted in order to produce brief tones that were 75 dB in intensity (i.e. measured from a height of 15 cm at two or more points above the chamber floor bars). The tone generator was controlled using Med-PC IV software (Med Associates, Inc., St. Albans, VT, USA) on a computer outside the room.

Gating protocols

In four separate sessions, two different IG protocols were used. In each session, the stimuli were presented in blocks of identical tone pairs. The protocols were used to examine the stability of gating and the effects of stimulus timing.

Protocol 1: paired-stimulus tests

The stability of gating was investigated by recording for three consecutive sessions. Prior to the first exposure to the paired