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Lesions of the Dorsomedial Striatum Disrupt Prepulse Inhibition

Lissandra C. Baldan Ramsey, Ph.D.¹, Meiyu Xu, Ph.D.¹, Nellie Wood³, and Christopher Pittenger, MD, Ph.D.^{1,2,*}

¹ Department of Psychiatry, Yale University School of Medicine, 34 Park Street, New Haven, CT 06508

² Interdepartmental Neuroscience Program, Yale University School of Medicine, 34 Park Street, New Haven, CT 06508

³ Middlebury College, Middlebury, VT

Abstract

Prepulse inhibition of startle (PPI) is an experimentally tractable measure of sensorimotor gating that can be readily evaluated in mice, rats, monkeys, and humans. PPI is the inhibitory effect of a low-intensity stimulus, the prepulse, on the startle response to a subsequent high-intensity stimulus. PPI has garnered great interest as a marker of clinically relevant information processing abnormalities, because it is impaired in such neuropsychiatric conditions as schizophrenia, Tourette syndrome, and obsessive compulsive disorder (OCD). Pathology of the basal ganglia has been described in all three of these disorders, and it is therefore of great interest to determine the role of the basal ganglia in PPI. Previous work in rats described a PPI deficit after excitotoxic ventral striatal lesions and a more subtle attenuation after caudodorsal lesion, but no effect of other large lateral dorsal lesions. However, previous studies have not specifically investigated the role of the dorsomedial striatum in PPI. We investigated this issue using excitotoxic lesions in mice. We describe a marked reduction in PPI, at a variety of prepulse intensities, after bilateral lesions of dorsomedial striatum. There was no effect of lesion on baseline startle or habituation. In contrast, comparably sized lesions of the central dorsal striatum had no effect on PPI. These results reveal a role for the dorsomedial striatum in prepulse inhibition, which may have relevance for the abnormalities observed in this region in such disorders as Tourette syndrome and OCD.

Keywords

striatum; dorsomedial; lesion; prepulse inhibition; mice; neuropsychiatric disorder

1. INTRODUCTION

A healthy nervous system engages a variety of mechanisms to suppress or “gate” irrelevant information in sensory, cognitive and motor domains, so that an individual can focus attention on the most salient stimuli in the environment (Braff and Geyer, 1990). Different neuropsychiatric disorders are characterized by a loss in the normal ability to suppress irrelevant information (Swerdlow and Sutherland, 2005). For example, patients with schizophrenia are unable to automatically filter or “gate” irrelevant thoughts and sensory

Correspondence: Christopher.pittenger@yale.edu 203-974-7675.

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stimuli from intruding into conscious awareness (McGhie and Chapman, 1961). In Tourette Syndrome, a breakdown in these gating mechanisms may contribute to the perceptual or psychic process experienced as a sensory tic or premonitory urge (Swerdlow and Sutherland, 2005). Attenuation of gating mechanisms may also contribute to the symptomatology of obsessive compulsive disorder (OCD; Schall et al., 1996).

Prepulse inhibition (PPI) of the startle reflex is a well-characterized and extensively studied model of sensorimotor gating that can be readily measured in rodents, in non-humans primates and humans (Willott et al., 1994, Paylor and Crawley, 1997, Braff et al., 2001, Davis et al., 2008, Swerdlow et al., 2008). The startle reflex is a rapid, stereotyped, reflexive response to sudden and intense auditory, visual, or tactile stimuli (Hoffman and Flesher, 1963, Swerdlow et al., 2008). In PPI, a weak prepulse stimulus, 30–500 msec prior to the startling stimulus, inhibits the reflex response. The amount of inhibition is used as an operational measure of sensorimotor gating (Swerdlow and Sutherland, 2005).

The acoustic startle reflex is mediated by brainstem nuclei (Davis et al., 1982, Li et al., 1998, Fendt et al., 2001, Yeomans et al., 2006). Prepulse inhibition involves modulation of this startle reflex by more rostral structures, including temporal and medial prefrontal cortex, the ventral striatum, the ventral pallidum and the pontine tegmentum (Koch and Bubser, 1994, Swerdlow et al., 1999, 2000, Arai et al., 2008). This circuitry provides a descending modulatory input to the primary startle circuit at the level of the nucleus reticularis pontis caudalis (NRPC) in the brainstem (Koch et al., 1993). Disturbances in PPI have been described in schizophrenia, Tourette syndrome, and OCD (Smith and Lees, 1989, Swerdlow et al., 1993, Castellanos et al., 1996, Braff et al., 2001, Swerdlow et al., 2001b, Hoening et al., 2005, Swerdlow and Sutherland, 2005).

Interestingly, these neuropsychiatric conditions are all characterized by pathology of the dorsal striatum (corresponding to the primate caudate and putamen). Caudate volume loss has been found in multiple studies in unmedicated, first-break schizophrenic patients (e.g. Brandt and Bonelli, 2008). Patients with Tourette syndrome have smaller caudate and putamen volumes and decreases in caudate metabolism (Peterson et al., 1993a, Eidelberg et al., 1997, Peterson et al., 2003), as well as interneuronal abnormalities in both caudate and putamen (Kalanithi et al., 2005, Kataoka et al., 2010). In OCD, numerous studies have documented elevated metabolism in the caudate nucleus in patients with OCD upon symptom provocation (reviewed in Maia et al., 2008, Menzies et al., 2008). PPI deficits are also seen early in Huntington's disease (Swerdlow et al., 1995), in which dorsal striatal pathology is prominent.

The contribution of the dorsal striatum to PPI is therefore of substantial interest; but it has been little studied. Ventral striatal-pallidal modulation of PPI has been examined more extensively (Kodsi and Swerdlow, 1995b, 1997b, c, Swerdlow et al., 2001a). Developmental manipulations that cause striatal damage can lead to deficits in PPI (e.g. Kodsi and Swerdlow, 1997a). An interesting study in rats showed that lesions of the ventral and caudodorsal striatum significantly decreased PPI, while other large lesions did not (Kodsi and Swerdlow, 1995a). However, this study did not examine the effect of dorsomedial striatal disruption; all lesions of the dorsal striatum were of the central and lateral regions. Functional differentiation between subregions of the dorsal striatum is increasingly appreciated (e.g. Yin and Knowlton, 2006), emphasizing the importance of explicitly interrogating the role of the dorsomedial striatum in modulating PPI. This is what we did in the current study, using excitotoxic lesions in mice.

2. EXPERIMENTAL PROCEDURES

2.1 Subjects

All experiments were conducted under the supervision of the Yale University Institutional Animal Care and Use Committee (Animal Welfare Assurance Number A3230-1). Food (standard laboratory chow) and water were available *ad libitum*. A total of 70 adult male C57Bl/6J mice were used in the study. Mice were 8–10 weeks old at the time of surgery and 14–16 weeks old at the time of testing. All animals were used in a water maze experiment (as in Lee et al., 2008) prior to PPI testing. All efforts were made to minimize the number of animals used and their suffering.

2.2 Stereotaxic surgery and lesions

Stereotaxic surgery was performed following standard procedures, under sterile conditions. Anesthesia was with pentobarbital (60 mg/kg in normal saline, intraperitoneal). Excitotoxic lesions were performed by manual infusion of NMDA (Sigma; 1.5 mg/ml in sterile saline) through a 0.5- μ l Hamilton syringe over the course of 2 to 3 min; control mice received an identical infusion of normal saline. Injectors were left in place for 60 s following infusion and then slowly removed. Targeting coordinates were determined from the atlas of Paxinos (Paxinos and Franklin, 2004) and refined empirically in pilot experiments. For dorsomedial striatal lesions, 0.1 μ l NMDA per side was infused ($N = 17$; anterior-posterior [AP], +0.74 mm; medial-lateral [ML], ± 1.6 mm; dorsal-ventral [DV], -3.0 mm). For central dorsal striatal lesions 0.1 μ l NMDA per side was infused ($N = 21$; AP, +0.5 mm; ML ± 2.7 mm; DV, -3.5 mm). Bilateral injections of saline using the same coordinates were done for the control group ($N = 17$ in each experiment).

2.3 Apparatus

Each startle chamber consisted of a nonrestrictive Plexiglas cylinder 5 cm in diameter, resting on a Plexiglas platform in an illuminated, ventilated sound-attenuating chamber (San Diego Instruments, San Diego, CA). A high-frequency speaker mounted 33 cm above the cylinder produced all acoustic stimuli. Mouse movements were detected and transduced by a piezoelectric accelerometer located under the cylinder, and then digitized and stored by a computer and interface assembly. Sixty-five 1-msec readings were recorded to obtain the amplitude of the animals' startle response to each stimulus, beginning at stimulus onset.

2.4 Test Session

PPI was assessed as previously described (Geyer and Dulawa, 2003). The test session began with a 5-min acclimation period, followed by four consecutive blocks of test trials. Broad-band background noise (65 dB) was continuously present throughout the experiment. Sound levels, both of background noise and of stimuli, were measured using the 'A' scale in units of dB (Geyer and Dulawa, 2003). Mice were exposed to eight different configurations of stimuli or "trials". "Pulse-alone" trials consisted of a 40-msec broad-band 120 dB noise burst and provide a reference, baseline startle.

There were six different types of "Prepulse" trials, in which a 20-msec broadband prepulse 6 dB, 12 dB, or 16 dB above background preceded the 120 dB startle pulse by 30 or 100 msec (onset to onset). "No Stimulus" trials consisted of only the background noise and were used to assess animals' spontaneous movement during the experiment. Trials were presented in four continuous blocks, separated by an average of 15 s (range: 7–23 s). Blocks one and four consisted of six consecutive Pulse Alone trials, while blocks two and three each consisted of six Pulse Alone trials, five of each kind of Prepulse trial, and five No Stimulus trials, intermingled in pseudo-random order. Thus, the entire 28-min session consisted of 64 test trials. Trials with excessive spontaneous movement in the 50 msec prior to the pulse, with a

noisy baseline, or with no appreciable response to the startle stimulus were excluded prior to data analysis. The response acquisition window was 65 msec.

2.5 Documentation of Lesions

After completion of behavioral testing, all mice were given a lethal overdose of pentobarbital sodium. Brains were rapidly removed and fixed overnight in 4% paraformaldehyde/PBS solution at 4°C. After fixation, brains were equilibrated with 30% sucrose and sliced on a microtome at 40 µm; slices were stored in cryoprotectant solution (30% glycerin, 30% ethylene glycol, 0.2 X PBS solution) at 4°C.

Lesions were documented by immunostaining for GFAP, which identifies regions of gliosis, as described previously (Lee et al., 2008). Floating sections were washed three times for 10 min with PBS solution, blocked with PBS/0.3% Triton/2% goat serum (Sigma) for 1 hour with gentle shaking, and then immunostained overnight for GFAP (rabbit polyclonal anti-GFAP IgG, Z0334, 1:500; Dako) and NeuN (mouse monoclonal anti-NeuN IgG, MAB377; 1:1,000; Chemicon International) in PBS/0.3% Triton. The following day, slices were rinsed twice in PBS/0.3% Triton and twice in PBS solution, stained for 1 h with secondary antibodies (Alexa Fluor 594 goat anti-rabbit IgG, A11037, Invitrogen, 1:300; Alexa Fluor 488 goat anti-mouse IgG, A11029, Invitrogen, 1:300) in PBS/0.3% Triton/2% goat serum, washed again three times in PBS/0.3% Triton, and mounted on glass slides. GFAP and NeuN immunoreactivity were visualized on an upright Nikon fluorescent microscope. Lesion extent was sketched freehand from photomicrographs of the lesions onto corresponding sections in the stereotaxic atlas by an experimenter who was unaware of the behavioral results.

2.6 Data Analysis

PPI was calculated from raw startle amplitude, which is in arbitrary units, for each prepulse intensity as $\%PPI = [\text{pulse alone} - \text{prepulse}] / \text{pulse alone} * 100$. PPI was calculated in blocks 2 and 3 using Pulse Alone trials for the same block. Little PPI was observed with the 30 ms inter-pulse interval, especially at low prepulse intensities; analysis was therefore restricted to data from trials with a 100 ms inter-pulse interval, which is commonly used in mice (Geyer and Dulawa, 2003). PPI was analyzed by Analysis of Variance with repeated measures (RM-ANOVA), with prepulse intensities as a within-subject factors and lesion as a between-subject factor. Baseline startle reactivity was analyzed by one-way ANOVA of Block 1 startle amplitude; similar analyses were done of 'pulse-alone' trials in Blocks 2 and 3. Startle habituation across the experiment was analyzed by RM-ANOVA of all Pulse-alone trials, with Block number (1–4) as a within-subject factor and lesion condition as a between-subject factor.

3. RESULTS

3.1 Dorsomedial lesions of the striatum impair PPI

Excitotoxic lesions of the dorsomedial striatum were produced by stereotaxic infusion of NMDA (see Methods); control mice received identical infusions of normal saline, and the experimenter was blind to lesion condition. PPI was measured with prepulses 6, 12, and 16 dB above background using standard methods, as previously described (Geyer and Swerdlow, 2001).

RM-ANOVA of %PPI with a 100 ms prepulse-pulse interval showed significant main effects of lesion (RM-ANOVA: $F[1,30]=5.74$, $p = 0.02$) and prepulse intensity ($F[2,60]=10.06$, $p = 0.000$), with no intensity X lesion interaction ($F[2,60] = 1.80$, NS; figure

1B). Similar effects were seen in Block 2 and Block 3 when analyzed separately (not shown).

Interpretation of PPI differences can be complicated by differences in baseline startle. We found no difference between lesioned and control mice in startle during the initial block of testing (figure 1C; ANOVA: $F[1,30] = 0.0002$; NS) or in blocks 2 or 3, during which PPI was assessed (figure 1C; block 2: $F[1,30] = 0.02$, NS; block 3: $F[1,30] = 0.18$, NS). Habituation was seen across the four blocks of testing (figure 1C; RM-ANOVA: main effect of block, $F[3,90] = 5.32$, $p = 0.002$), but there was no effect of lesion ($F[1,90] = 0.26$, NS) or block X lesion interaction ($F[3,90] = 1.06$, NS). There was no effect of lesion on animals' weight ($F[1,30] = 0.31$; NS).

Following the experiment, animals were sacrificed and their lesions documented using GFAP immunohistochemistry to identify areas of gliosis. A summary of all lesions is shown (figure 1A); no animals had to be excluded from analysis in this experiment because of misplaced lesions.

3.2 Central dorsal lesions of the striatum do not affect PPI

In a second cohort of mice, lesions of the central dorsal striatum were produced using an identical approach but different stereotaxic coordinates. PPI in lesioned and control mice was tested using an identical protocol.

We found no effect of central dorsal lesions on PPI (RM-ANOVA: $F[1,33] = 0.30$, NS). As in the first experiment, a main effect of prepulse intensity was found ($F[2,66] = 16.39$, $p < 0.001$). There was no significant interaction between intensity and lesion ($F[2,66] = 2.05$, $p > 0.1$; figure 2B). Similar data were seen when blocks 2 and 3 were analyzed separately (not shown).

As in the first experiment, there was no effect of lesion on baseline startle (figure 2C; $F[1,33] = 0.32$, NS) or on habituation across the four blocks (figure 2C; RM-ANOVA: main effect of block, $F[3,99] = 3.83$; $p = 0.01$; main effect of lesion, $F[1,33] = 0.001$, NS; lesion X block interaction, $F[3,99] = 1.10$, NS). There was no effect of lesion on animals' weight ($p > 0.05$).

Lesions were again documented by immunohistochemistry. Three lesioned animals were excluded from analysis because of mis-targeted lesions. A summary of lesions included in this analysis is shown in figure 2A.

4. DISCUSSION

Neuropsychiatric disorders such as schizophrenia, Tourette syndrome, and obsessive compulsive disorder are characterized by a loss in the normal ability to suppress or "gate" irrelevant information from external or internal sources (McGhie and Chapman, 1961, Schall et al., 1996, Swerdlow and Sutherland, 2005). PPI is a widely studied experimental measure of sensorimotor gating that is used as a simplified model of this process; PPI is impaired in all three disorders (Smith and Lees, 1989, Swerdlow et al., 1993, Castellanos et al., 1996, Braff et al., 2001, Swerdlow et al., 2001b, Hoenig et al., 2005, Swerdlow and Sutherland, 2005). Disturbances in motor and cognitive functions of the striatum are also seen in schizophrenia, TS, and OCD (Peterson et al., 1993a, Peterson et al., 1993b, Eidelberg et al., 1997, Peterson et al., 2003, Kalanithi et al., 2005, Brandt and Bonelli, 2008, Menzies et al., 2008, Kataoka et al., 2010). Any contribution of striatal function to PPI is consequently of substantial interest for understanding potential links between perturbed brain function and PPI deficits in such neuropsychiatric conditions.

The modulation of PPI by the ventral striatum and ventral pallidum has been intensively studied (Swerdlow et al., 1990, Kodosi and Swerdlow, 1995a, 1997b, c, Swerdlow et al., 2001a, Arai et al., 2008). In contrast, the contribution of the dorsal striatum, and particularly of the dorsomedial striatum, to PPI has received relatively little attention. We found a significant deficit in PPI after NMDA lesions of the dorsomedial striatum in C57Bl/6J mice (figure 1).

This effect was quite specific: comparably sized excitotoxic lesions of a neighboring central region of the dorsal striatum had no significant effect on PPI (figure 2). This dissociation emphasizes functional differentiation along the medial-lateral axis of the dorsal striatum (Yin and Knowlton, 2006). It also may explain why a similar effect of dorsal striatal lesions has not been seen in previous studies in rat – though of course there may be an intra-species difference in this dependence; relatively few studies have examined the neural circuitry of PPI in mice. One systematic study of the effects of dorsal striatal lesions along the anterior-posterior axis in rats found minimal effect, with only a small deficit in PPI after caudodorsal lesions; but lesions in this study were targeted to the central and lateral regions of the dorsal striatum and did not affect the dorsomedial region targeted here (Kodosi and Swerdlow, 1995a). The absence of any effect on PPI after our central dorsal lesions (figure 2) is therefore consistent with the finding, in rats, that anterior and central dorsolateral lesions similarly had no effect on PPI (Kodosi and Swerdlow, 1995a).

Interestingly, in this earlier study both excitotoxic ventral striatal lesions and larger dorsolateral lesions increased startle amplitude (Kodosi and Swerdlow, 1995a). In contrast, the smaller lesions used here, in mice, had no effect on baseline startle (see figures 1C, 2C). It is unclear whether this discrepancy relates to the specifics of the lesions, to a species difference, or to some other environmental or experimental variable. It is clear that there are differences in the mechanisms and modulators of PPI between mice and rats, and even between different mouse strains (Swerdlow et al., 2008).

Most studies of the role of the basal ganglia in PPI have focused on the accumbens shell and core (Swerdlow et al., 1990, Kodosi and Swerdlow, 1995a, 1997b, Alsene et al., 2010), and the corresponding regions of the pallidum (Swerdlow et al., 1990, Kodosi and Swerdlow, 1995a, b, 1997c, Sipes and Geyer, 1997, Swerdlow et al., 2001a). Infusion of a GABA_A antagonist into the ventral pallidum produces a deficit in PPI, and infusion of GABA_A agonist blocks the PPI deficit produced by increased mesolimbic dopaminergic activity, consistent with the contribution of this pathway to normal PPI (Swerdlow et al., 1990). GABAergic projections from the caudo-dorsal pallidum reach the pedunculopontine tegmental nucleus (PPTg) (Moriizumi and Hattori, 1992) and from the PPTg, inhibitory cholinergic projections innervate the nucleus reticularis pontis caudalis (NRPC) (Koch et al., 1993). The NRPC is a key structure of the startle reflex pathway (Fendt et al., 2001, Yeomans et al., 2006).

The most medial region of the dorsal striatum receives input from limbic cortices, similarly to the nucleus accumbens, and projects to similar ventral and lateral regions of the lateral globus pallidus and of the substantia nigra pars reticulata (Gerfen, 2004). It is therefore possible that the contribution of the medial striatum to the regulation of PPI is analogous to the previously established role of the nucleus accumbens. Further investigations of the connectivity of this region and how it interacts with other circuitry implicated in PPI will be required to resolve similarities and differences between the contributions of the two striatal subregions.

While many studies have examined PPI in genetically modified mice, the anatomy of the underlying circuitry has been examined primarily in rats. Moving studies such as this into

mice carries benefits for future work. New techniques allow the targeting of specific cellular subpopulations, such as interneurons, in defined brain regions in mice (Sohal et al., 2009). Such approaches are of particular interest in this context because of the recent appreciation of the potential importance of interneuronal pathology in disorders such as TS (Kalanithi et al., 2005, Kataoka et al., 2010). Clarifying the circuit underlying PPI specifically in mice opens the door for the application of cell type-specific manipulations that are not possible in other systems.

In conclusion, we found that excitotoxic lesions of the dorsomedial striatum impair PPI in mice, while similar lesions of the central dorsal striatum do not. Abnormalities in the dorsal striatum are seen in various neuropsychiatric disorders in which PPI deficits are seen. Understanding the precise neuroanatomical connectivity and neurochemistry of this circuitry, and how it contributes to normal information gating, may bring new insights about the neuropathophysiology of these disorders.

5. CONCLUSION

Our results showed that disruption of the medial aspects of the striatum in mice caused significant deficits in prepulse inhibition, a measure of sensorimotor gating. This finding adds to the knowledge about the neurophysiology of these neural substrates and circuitry involved with neuropsychiatric disorders.

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FIGURE 1. Effect of dorsomedial striatal lesions on PPI

A. Excitotoxic dorsomedial striatal lesions were made by stereotaxic infusion of NMDA in mice, as described in the text. Lesion extent was documented by immunohistochemistry for GFAP; regions of gliosis were manually outlined. Superimposed regions of lesion for all mice used in this experiment are shown. **B.** Lesioned mice showed impaired PPI at all frequency relative to controls. See text for statistical comparisons. **C.** Lesions had no effect on startle on Pulse-Alone trials over the course of the four blocks of trials. PPI data are drawn from Blocks 2 and 3. See text for statistics.

FIGURE 2. Effect of central dorsal striatal lesions on PPI

A. Lesions were produced and documented as in Figure 1. Region of lesion for all mice used in this experiment are shown; three mice were excluded due to an absence of clear bilateral lesions in the target region. **B.** These lesions had no effect on PPI at any prepulse intensity. See text for statistical comparisons. **C.** Similarly, these lesions had no effect on absolute startle magnitude across the course of the four blocks of the experiment.