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Excitotoxic lesion of the posterior part of the dorsal striatum does not affect the typically dopaminergic phenomenon of latent inhibition in conditioned taste aversion

Andrés Molero-Chamizo*

Department of Psychobiology, University of Granada, Campus Cartuja 18071, Spain

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ABSTRACT

The stimulation or blockade of dopaminergic activity interrupts or increases, respectively, the phenomenon of latent inhibition in different paradigms. Furthermore, the involvement of the nucleus accumbens in latent inhibition has been demonstrated in several learning paradigms, including conditioned taste aversion. However, the role of the dorsal striatum in the pre-exposure effect on the acquisition of taste aversion remains unclear. In order to determine whether this region of the striatum is a structure necessary for latent inhibition of conditioned taste aversion, excitotoxic lesions were made in the posterior part of the dorsal striatum of Wistar rats. Subsequently, half of the animals was pre-exposed to the flavor, and the magnitude of the taste aversion was compared to that of sham animals pre-exposed and non-pre-exposed to the same flavor. The results showed that the excitotoxic lesion in this area of the dorsal striatum, compared to sham animals, left latent inhibition of the conditioned taste aversion intact. These data suggest that the posterior part of the dorsal striatum is not necessary for the acquisition of latent inhibition, at least in the conditioned taste aversion paradigm.

1. Introduction

Different dopaminergic manipulations alter the phenomenon of latent inhibition (Bethus et al., 2003; Norman and Cassaday, 2004; Bethus et al., 2006), which consists of a reduced conditioned response to a stimulus previously pre-exposed and non-reinforced (Lubow, 1989). Thus, amphetamine infused into the nucleus accumbens disrupts latent inhibition (Weiner et al., 1988; Nelson et al., 2012), whereas dopaminergic antagonists into the nucleus accumbens significantly enhance this learning (Weiner et al., 1987; Christison et al., 1988). The dopaminergic activity of the anterior part of the dorsal striatum also appears to be involved in latent inhibition (Meyer et al., 2009), for example in the conditioned olfactory aversion paradigm (Jeanblanc et al., 2003, 2004; Peterschmitt et al., 2005). Nevertheless, in the latent inhibition of conditioned taste aversion (CTA) paradigm the involvement of the striatum has not been firmly defined and the results of the research remain unclear. In this regard, the administration of amphetamine into the dorsal striatum seems to disrupt the latent inhibition of CTA (Ellenbroek et al., 1997), but in this aversive paradigm the absence of adenosine receptor in the striatum (which is thought to regulate dopaminergic activity in this structure) does not affect the expression of latent inhibition (Singer et al., 2013). Moreover, a correlation has been observed between latent inhibition and reduced striatal c-Fos expression in the CTA paradigm (Turgeon and Reichstein, 2002), which has been interpreted as support for the hypothesis of a possible inhibitory role of the striatum in the expression of latent inhibition. The discrepant results on latent inhibition of CTA are also common in relation to the ventral striatum. Latent inhibition of CTA is as sensitive to systemic amphetamine as in the conditioned emotional response paradigm (Russig et al., 2003), but in this case there is a discrepancy with respect to the role of the ventral striatum. Counter to the expected disruption which would be predicted based on conditioned emotional response studies (Tai et al., 1995), shell accumbens lesions enhanced latent inhibition when tested in a CTA procedure (Pothuizen et al., 2006). Moreover, apparently only with a CTA procedure can latent inhibition be abolished by amphetamine treatment (injected ip) confined to stimulus pre-exposure (Bethus et al., 2006), in contrast to the results typically obtained with the conditioned emotional response paradigm. Similarly, hippocampal lesions also have contrary effects on latent inhibition when tested with CTA (Reilly et al., 1993).

* Correspondence to: Psychobiology Area, University of Huelva, Campus El Carmen, 21071 Huelva, Spain. Tel.: +34 959218478; fax: +34 959219201.
E-mail address: andres.molero@dpsi.uhu.es

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Table 1
Stereotaxic coordinates.

GROUP	A–P 1	A–P 2	M–L 1	M–L 2	D–V 1	D–V 2
Striatum	+0.2	−0.4	±3	±3.2	+5.8	+5.4
Sham	+0.2	−0.4	±3	±3.2	+5.8	+5.4

A–P, anterior–posterior axis; M–L, medial–lateral axis; D–V, dorsal–ventral axis.

In addition, excitotoxic lesions and other more selective methods used to manipulate dopamine function in striatal regions also yield discrepant results on latent inhibition. Since excitotoxic lesions are not selective to dopaminergic neurons, different results can be expected when 6-OHDA lesions are targeted to the shell versus core accumbens. Thus, in contrast to the expected disruption of latent inhibition of the conditioned emotional response observed with shell accumbens lesions (Tai et al., 1995), 6-OHDA lesions enhanced latent inhibition as measured in a closely similar conditioned emotional response procedure (Nelson et al., 2011).

In general, it appears that the involvement of the dorsal striatum in the phenomenon of latent inhibition depends on the learning paradigm and the specific brain manipulation used (Konstandi and Kafetzopoulos, 1993), or region of the dorsal striatum targeted by the study (Jeanblanc et al., 2003; Díaz et al., 2014). Therefore, in order to determine whether the striatum is a necessary structure for acquiring latent inhibition of CTA, the current study analyzed the effect of a located striatal lesion using the classic paradigm of latent inhibition of CTA.

2. Materials and methods

2.1. Animals

Thirty-one adult male Wistar rats (280–310 g) were individually housed in boxes measuring 30 cm × 15 cm × 30 cm. Throughout the behavioral procedure, the animals were exposed to a daily 12 hours light-dark cycle (lights on from 9:00 to 21:00), and the temperature conditions were kept constant at 23 °C. Food was provided ad libitum, and the availability of fluid was restricted to 15 min daily throughout the behavioral procedure. The procedure was approved by the Ethics Committee for Animal Research of the University of Granada, and was conducted in accordance with both the NIH Publications (N° 80-23) of the National Institute of Health Guide (United States) for the care and use of laboratory animals revised 1996, and the European Communities Council Directive of 24 November 1986 (86/609/EEC). The National legislation, in agreement with this Directive, is defined in Royal Decree N°. 1201/2005.

2.2. Surgery

Animals were anaesthetized with an intraperitoneal (i.p.) injection of sodium pentobarbital (1 mL/kg), and placed in a stereotaxic apparatus for surgery (Stoelting Co. Instruments, Wood Dale, IL, USA). The incisor bar was set 3.3 mm below the interaural line. After a longitudinal incision was made to expose the skull, bregma and lambda points were leveled in the horizontal plane, and two trepanations were made in each hemisphere using bregma as a reference point to induce an extensive lesion in the striatum. The stereotaxic coordinates were taken from the atlas of Paxinos and Watson (2005) (Table 1). All animals, except sham groups, received two successive injections of N-methyl-D-aspartate (NMDA) (0.6 μL; 0.077 M) in each trepanation of each hemisphere, through an injection cannula (0.3 mm exterior × 0.15 mm interior) connected to a micro-syringe (Hamilton, 10 μL). The neurotoxin was injected at a rate of 1 μL/min using an injection pump (Harvard, USA). The cannula remained at the lesion site for 2 min after the injections to allow for diffusion of the neurotoxin. Immediately thereafter, the cannula was removed and the incision sutured. The procedure was identical for sham groups, except that no neurotoxin was injected through the cannula. Rats were allowed a postoperative recovery period of seven days in which water and food was available ad libitum.

2.3. Behavioral procedure

Rats were randomly distributed among the following four groups: PE-St, pre-exposed to the flavor and striatal lesion ($n = 9$); NPE-St, non-pre-exposed and striatal lesion ($n = 9$); PE-Sh, pre-exposed and sham lesion ($n = 7$); NPE-Sh, non-pre-exposed and sham lesion ($n = 6$). All animals were deprived of fluid for a daily period of 23 h 45 min throughout the experiment. The mean consumption of water by each group in the two-day baseline was recorded. Subsequently, the pre-exposed groups were pre-exposed for two days to a sodium saccharin solution (0.1%) for 15 min. The non-pre-exposed control groups had access to water on that period. On the fifth day all groups were exposed to saccharin solution for 15 min, and the consumption was recorded. Twenty minutes later, all animals received an injection of lithium chloride (LiCl) (0.15 M, 2% of body weight, i.p.). After one day of recovery with water (15 min), all animals were exposed again to saccharin solution for 15 min and the consumption was also recorded. Table 2 summarizes the behavioral procedure.

2.4. Histology

When the experiments were completed, brains were removed and stored in 10% formalin solution and subsequently cryosectioned (Erma-422, Tokyo) at 45 μm. The slides were stained with cresyl violet and examined under an optical microscope (CH-30, Olympus). Images of the slides were captured with a TV Olympus camera (U-PMTVC, Japan).

2.5. Statistical analysis

The effect of the striatal lesion on latent inhibition was analyzed using a 2 × 2 factorial design, with one inter-group factor with two levels (*striatal lesion* and *sham*) and another inter-group factor with two levels (*pre-exposure* and *non-pre-exposure*). Data from pre-exposure and conditioning days were analyzed by a factorial ANOVA. The significant factors were analyzed using a one-way ANOVA. Saccharine consumption on the test day was analyzed by a factorial analysis of covariance (ANCOVA). The significant factors were analyzed by one-way ANCOVA. Where interactions were significant, Newman–Keuls post hoc tests were applied to analyze differences.

3. Results

3.1. Anatomical results

The neurotoxin induced a lesion in all animals on the dorsal area of the striatum, with a slight extension toward the ventral striatum in a few cases without reaching the nearby bed nucleus of stria terminalis. Lesions were comparable in both groups. Cell loss and microglial proliferation were observed in the dorsal striatum, and specifically in the more medial cell bodies adjacent to the lateral ventricles. The extension of the lesion induced by the neurotoxin was variable, although in all cases the dorsal region of the striatum was lesioned, and the larger degeneration was selectively located in the dorsomedial region, without a significant extension to the lateral areas of the dorsal striatum. Ventral striatum, particularly the specific sub-regions of nucleus accumbens, was not lesioned in any animal. No excitotoxic lesion was found outside the intended