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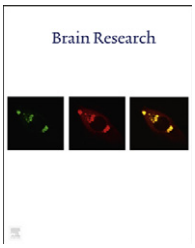

Research Report

The anterior claustrum and spatial reversal learning in rats

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ARTICLE INFO

Article history:
Accepted 7 January 2013
Available online 11 January 2013

Keywords:
Claustrum
Excitotoxic lesion
Spatial reversal learning
Working memory
Latent inhibition
Behavioral flexibility

ABSTRACT

The claustrum is a small structure of poorly understood function situated subcortically in the basal forebrain. The fact that it is extensively and reciprocally connected with the cerebral cortex has led to suggestions that it is involved in coordination of cortical activity. In this study, we created excitotoxic lesions to the anterior claustrum of rats and tested performance on three tasks that involve neural processing in one or more frontal and limbic cortical structures. We tested reversal learning and spatial working memory in a water maze and tested latent inhibition using conditioned taste aversion. Lesioned rats were not impaired at acquiring the initial location of the platform in a water maze, but were impaired at acquiring a switched location in the reversal phase. The lesioned rats also exhibited an increased rate of perseverance errors compared to control rats during reversal. Lesioned rats were not impaired in the working memory task or latent inhibition. These results indicate that cell loss in the claustrum may lead to deficits in behavioral flexibility, and are consistent with theories of claustral function that suggest it may help coordinate information necessary for at least some cortical-dependent tasks.

1. Introduction

It has been hypothesized that the claustrum plays a critical role in the integration of information across sensory modalities during perceptual processing (Crick and Koch, 2005), or that the claustrum provides integration of sensory and motor information (Edelstein and Denaro, 2004). The main rationale for this type of hypothesis is based on the most salient feature of claustral anatomy, a broad reciprocal connectivity between the claustrum and the neocortex, including the sensory and motor areas (Fernández-Miranda et al., 2008; LeVay and Sherk, 1981a; Pearson et al., 1982; Smith and Alloway, 2010; Tanné-Gariépy et al., 2002). However, although claustral neurons respond to visual, acoustic, and somatic stimuli (Clarey and Irvine, 1986; LeVay and Sherk, 1981b; Olson and Graybiel, 1980; Sherk and LeVay, 1981) individual claustral neurons of primates have unimodal response characteristics (Remedios et al., 2010). This suggests little integration of information across sensory modalities in the claustrum. Moreover, detailed anatomical study of rats found little possibility of integration across primary whisker somatosensory and motor cortical areas within the claustrum because the whisker somatosensory area does not project to it (Smith et al., 2012). Thus, while the claustrum may process sensory and/or motor representations, those representations do not universally appear to be integrated within the claustrum.

The claustrum is extensively and reciprocally connected to many cortical and subcortical structures in addition to those primarily involved in sensation or movement (Fernández-Miranda et al., 2008; Zhang et al., 2001), suggesting that the claustrum may indeed have functions other than

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0006-8993/$ - see front matter
http://dx.doi.org/10.1016/j.brainres.2013.01.014

sensory and motor integration. The connections are arranged so that the anterior, central, and posterior sections of the claustrum respectively have denser connections with the anterior, central, and posterior areas of the cortex (Fernández-Miranda et al., 2008; Kowiański et al., 1998). This topographical arrangement of connections may result in different functional zones within the claustrum (Kowiánski et al., 2000). Smythies et al. (2012) recently suggested that the claustrum works to augment synchronization of activity of different areas of the cortex, promoting integration of neural activity within the time domain. This hypothesis has the advantage of not being concerned with the information content of the activity being processed, and thus the proposed mechanism can affect the function of the multiple cortical connections to the claustrum.

Development of an effective claustral lesion in an animal model would be instrumental in assessing theories of claustral function. A complete and selective lesion of the claustrum is difficult to accomplish with standard methods due to its complex morphology and proximity to neighboring cortical structures. In rats however, the anterior section of the claustrum is vulnerable to experimental lesion. The rat anterior claustrum is located lateral to the forceps minor of the corpus callosum and medial to the orbital cortex. At this location, the anterior claustrum is approximately 1 mm deep. The thickness of the anterior claustrum and location adjacent to white matter make it vulnerable to targeted microlesion with infusion of excitotoxin. Thus we have studied the function of the anterior section of the claustrum in rats using a lesion to deficit correlation strategy.

We have tested the effect of lesions to the anterior claustrum on tasks that are sensitive to dysfunction in frontal cortical areas that connect to the anterior claustum, and have been proposed to be translational models of behavioral and cognitive deficits in human disease. The densest connections of the anterior claustrum in rats are with the nearby orbitofrontal cortex, and there is also connectivity with prefrontal, motor, and insular cortices as well as subcortical structures such as the amygdala and nucleus accumbens (Zhang et al., 2001). We have used reversal of operant place conditioning in a water maze, spatial working memory (i.e. delayed matching to place) at short and long delay periods, and latent inhibition.

Spatial reversal conditioning involves subjects learning a target location during a series of acquisition trials, and then learning a new target location in the opposite quadrant of the maze. Subjects are assessed on how effectively they acquire knowledge of the new location and whether they persist in seeking the target in the original location (Vorhees and Williams, 2006). The task requires suppression of an initial response in order to execute a new behavior for the desired outcome. Reversal learning and other tests of behavioral and cognitive flexibility are frequently impaired in disorders associated with the frontostriatal circuits (Izquierdo and Jentsch, 2012; Zald and Andreotti, 2010) and particularly with impairment of the orbitofrontal cortex (Boulougouris et al., 2007; Ragozzino, 2007; Schoenbaum et al., 2002; Schoenbaum et al., 2003). To study spatial working memory, the location of a goal location remains the same for a consecutive pairing of sample–test trials, and then the location is changed (Vorhees and Williams, 2006). The task requires subjects to maintain a representation of the target location from sample to test, and the delay between the sample and test can be varied. Delay-dependent impairments in working memory have been found after damage to the prelimbic and infralimbic areas of the medial prefrontal cortex (Dalley et al., 2004; Delatour and Gisquest-Verrier, 1999) and associated thalamic nuclei (Bailey and Mair, 2005). Latent inhibition occurs when a stimulus is presented prior to being presented with an unconditioned stimulus, and this retards the development of a conditioned response (Lubow, 1973). Frontal cortical structures are involved in both enabling and disrupting latent inhibition, and disruption of latent inhibition occurs in diseases of the frontal cortex such as schizophrenia (Weiner, 2003).

2. Results

2.1. Histology

Fig. 1 contains photomicrographs of a typical lesion included in the study compared to a control brain (Fig. 1A) and drawings that show the extent of the lesions on all rats included in the analyses (Fig. 1B). Each layer of gray in Fig. 1B represents the lesioned area of a single rat, indicating that the damage in common to the lesion group of rats was to the anterior claustrum. Rats sustained bilateral lesions to the anterior claustrum, with most damage sustained in the dorsomedial region. Two rats were included that had cell loss extending unilaterally into the anterior portion of the lateral orbital cortex. Removal of these rats from the statistical analysis did not reduce the size of any of the statistically reliable effects reported below. Fourteen rats were excluded from analysis due to missed lesions. There were 10 rats in the lesioned group and 10 rats in the control group included in the statistical analysis.

2.2. Reversal of operant place conditioning

A mixed-model ANOVA on distance swam during the water maze acquisition trials including the reminder trial after the acquisition probe test (Fig. 2) showed that the rats swam significantly less distance to find the goal platform as the trials progressed ($F(12,216)=14.76$, $p<0.001$). There was no difference between the lesioned and control group rats ($F(1,18)=0.01$, *ns*) and no interaction between group and acquisition trial ($F(12,216)=1.12$, *ns*).

In the spatial reversal trials, the lesioned group rats took a significantly longer distance to find the new platform location than controls (Fig. 3A; $F(1,18)=4.70$, $p=0.044$). The subjects overall swam shorter distances as the trials progressed ($F(1.86,33.42)=20.28$, $p<0.001$), and there was no significant interaction between group and reversal trial ($F(1.86,33.42)=0.60$, *ns*). Mauchly's test indicated that the assumption of sphericity was violated in the repeated measures variable (i.e. the trials variable) so the degrees of freedom of statistical tests involving that variable were corrected using the Greenhouse–Geissser estimate.

Also during the reversal trials the lesioned rats persevered with a greater frequency of crossings of the original acquisition