Neuroscience Letters xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Single unit activity in the lateral septum and central nucleus of the amygdala in the elevated plus-maze: A model of exposure therapy?

Earl Thomas*, Debra Burock, Kimberly Knudsen, Erin Deterding, Elna Yadin

Department of Psychology, Bryn Mawr College, Bryn Mawr, PA 19010, United States

HIGHLIGHTS

- We recorded unit activity in the septum and amygdala on the elevated plus-maze.
- Unit activity in the lateral septum was increased on the open arm.
- Unit activity in the central nucleus of the amygdala was decreased on the open arm.
- We suggest that LS inhibition of activity in CeA may allow for adaptive behavior on the open arms.
- This may have implications for the certain forms of psychotherapy in humans.

ARTICLE INFO

Article history:
Received 11 March 2013
Received in revised form 21 May 2013
Accepted 22 May 2013

Keywords:
Lateral septum
Amygdala
Central nucleus
Single-unit
Elevated plus-maze
Anxiety

ABSTRACT

The central nucleus of the amygdala (CeA) is a major output region of the amygdala involved in organizing the expression of fear. There is also evidence that the lateral septum (LS) provides inhibitory control of neurons in CeA and is involved in the relief of fear. This study examined single unit activity in the lateral septum (LS) and the central nucleus of the amygdala (CeA) in the open and closed arms of the elevated plus-maze, a highly validated animal model of fear and anxiety. The general presumption is that animals normally avoid the open arms because the open arms are relatively more anxiety provoking than the closed arms which represent relative safety. It was expected that neurons in CeA would increase their activity in the open arms relative to the closed arms indicative of increased anxiety and that LS neurons would decrease their activity on the open arms. Contrary to expectations it was found that the preponderance of units in CeA decreased their firing rates on the open arms compared to the closed arms. An increase in firing rates in LS was seen in the open arms compared to the closed arms. The data suggest that when animals are placed on the open arms a compensatory process takes place to suppress fear so that the animal can engage in adaptive behavior. We liken this process to that which takes place in exposure therapy for phobias in humans which involves the inhibition of fear resulting from Pavlovian extinction.

1. Introduction

There is substantial evidence that the central nucleus of the amygdala (CeA) is a major output region of the amygdala involved in organizing the expression of fear [9,21]. There is also evidence that the lateral septum (LS) provides inhibitory control of neurons in CeA and is involved in the relief of fear [17]. LS appears to be a major component of a system that provides regulatory control over the amygdala by a negative feedback mechanism [17]. The opposing roles of these two structures may be seen in stimulation experiments, lesioning experiments, and in single-unit recording experiments.

When the LS is stimulated, a diminution of somatic, visceral, and behavioral responses associated with fear is seen. For example, heart rate, blood pressure, respiration, scanning and vigilant behavior, the startle response, ulceration, and corticosteroid release are all decreased upon LS stimulation [4,7,16,22]. These effects may be characterized as anxiolytic. On the other hand, stimulation of CeA yields sympathetic ("fight or flight") autonomic responses that may be characterized as anxiogenic or anxiety-causing. When the CeA is stimulated, heart rate, respiration, gastric ulcers, and corticosteroid release are all increased. Behaviorally, increases are seen in alertness, scanning, vigilant behavior, urination, defecation, grooming, the freezing response and the startle response [5,8].

The opposite relationship of the two regions to anxiety may also be seen in lesion experiments. LS lesions are anxiogenic in

* Corresponding author at: Department of Psychology, Bryn Mawr College, 101 N. Merion Avenue, Bryn Mawr, PA 19010, United States. Tel.: +1 610 526 5013; fax: +1 610 526 7476.
E-mail address: ethomas@brynmawr.edu (E. Thomas).

0304-3940/$ – see front matter © 2013 Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.neulet.2013.05.078

rats [6] whereas lesions of the central nucleus of the amygdala are anxiolytic [23].

In single unit recording experiments employing Pavlovian fear conditioning, unit activity in LS was decreased in the presence of a conditioned exciter of fear whereas it was increased in the presence of a conditioned inhibitor of fear [20], Recent research indicates that increased unit activity the medial subdivision of CeA (CEm) reflects fear in a variety of paradigms including Pavlovian fear conditioning [1]

The elevated plus-maze is a commonly used model for assessing anxiety in rats and therefore may serve as a useful paradigm for looking at cellular activity in these structures related to fear. This study, employing male albino rats as subjects, examined the neural activity in LS and CEm in the open and enclosed arms of the elevated plus-maze. The general presumption is that animals normally avoid the open arms since the open arms are relatively more anxiety provoking than the enclosed arms which represent relative safety to the animal. Therefore it might be expected that neurons in CEm would increase their activity in the open arms relative to the enclosed arms indicative of increased anxiety. Conversely it might be expected that LS neurons would decrease their activity on the open arms.

2. Material and methods

2.1. Subjects

The subjects were male Sprague-Dawley albino rats (Harlan, Frederick MD) weighing 250–300 g. Animals were individually housed in a light and temperature controlled colony. The animals were maintained on a 12 h light/dark cycle. They were provided with *ad libitum* food and water. Care and use of animals were approved by the Institutional Animal Care and Use Committee and experiments were carried out in accordance with the *National Institutes of Health Guide for the Care and Use of Laboratory Animals*.

2.2. Surgery

Animals were anesthetized with sodium pentobarbital (42 mg/kg, i.p.). Recording electrodes were chronically implanted into the lateral septum (LS) and Central Nucleus of the Amygdala (CEm) using standard stereotaxic procedures. The implantation coordinates for the LS were AP 0.3 mm, Lat 0.7 mm, DV 6.0 mm. For CEm the coordinates were AP −2.2 mm. Lat 4.0 DV 8.0 [12] The recording electrode bundle contained eight wires measuring 50 μm in diameter (NB Labs; Denison, TX). Four anchoring screws were inserted into each animal's skull and a grounding wire was wrapped around one of the screws. The electrode assembly was secured to the skull by means of dental cement. Animals were returned to the colony to recover for 2 weeks prior to testing. Seven animals were implanted with a single probe in CEm, seven animals were implanted with a single probe in LS, and 6 animals were implanted with two recording probes one in CEm and one in LS

2.3. Unit recording

Each implanted electrode was connected to a plug containing field effect transistors arranged in a voltage follower configuration. This configuration minimizes undifferentiated multiple unit activity and virtually eliminates movement artifact as well as EMG artifact. The signal was passed through a bandpass filter (500–3000 Hz) and a high gain amplifier (A–M instruments model 1800). The final gain on the amplifiers was 10,000. The signal from each unit was monitored on a digital storage oscilloscope and recorded on magnetic tape and analyzed online by a commercial software package (CED Electronics: Spike2) which isolated the units of interest using a template matching algorithm. After the data were collected the waveforms of selected units were reexamined, off line, by eye and subjected to a principle components analysis using the cluster cutting software. Units that met at least a 3:1 signal to noise ratio were included in the experiment.

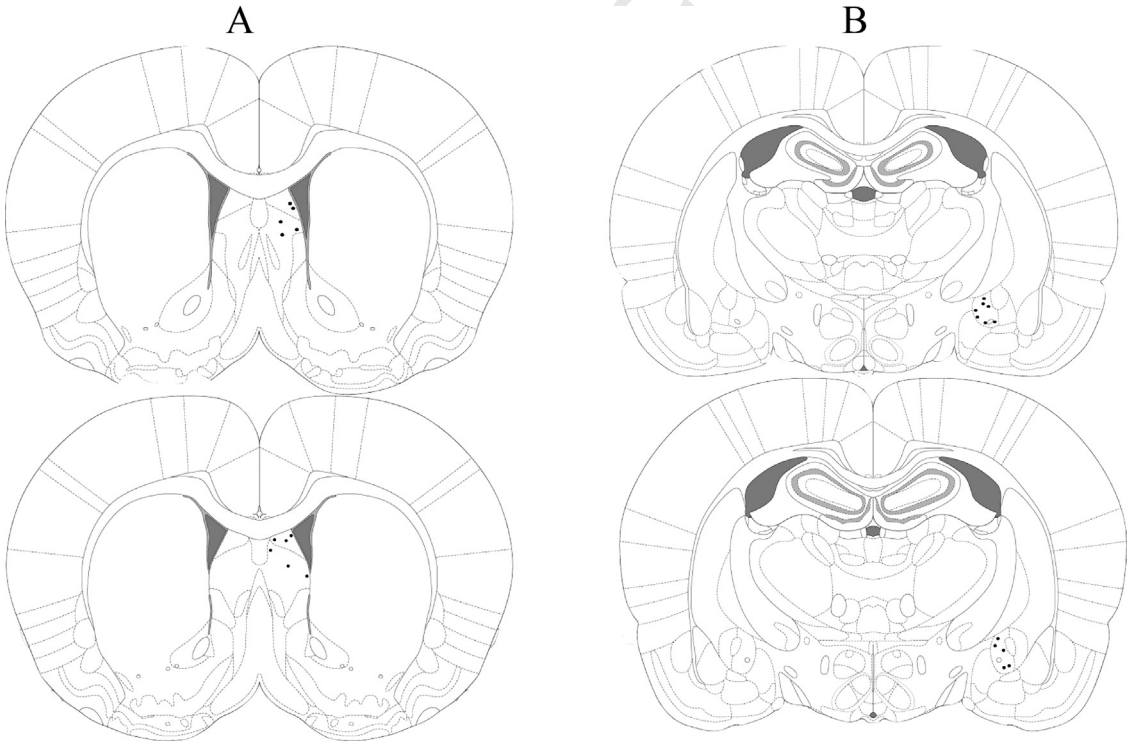

Fig. 1. Schematic depiction of recording sites in LS (A) and CEm (B).
Figures are from Paxinos and Watson [12].

Please cite this article in press as: E. Thomas, et al., Single unit activity in the lateral septum and central nucleus of the amygdala in the elevated plus-maze: A model of exposure therapy? Neurosci. Lett. (2013), http://dx.doi.org/10.1016/j.neulet.2013.05.078