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Convergence of nociceptive information in the forebrain of female rats: Reproductive organ response variations with stage of estrus

Harpreet K. Chadha, Charles H. Hubscher *

Department of Anatomical Sciences and Neurobiology, University of Louisville, Louisville, KY 40292, USA

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Abstract

Neurons in the preoptic area (POA) of the hypothalamus and the bed nucleus of stria terminalis (BST) play an important role in the neuroendocrine control of the reproductive cycle, mating behaviors and nociception. Single unit extracellular recordings were performed in the POA and BST region of 20 urethane anesthetized female rats during either the proestrus (elevated levels of estrogen/progesterone) or metestrus (low circulating hormones) stage of the estrous cycle. A total of 118 neurons in the POA and 65 neurons in the BST responded to the search stimuli, bilateral electrical stimulation of the viscerocutaneous branch of the pelvic nerve and/or sensory branch of the pudendal nerve (i.e., dorsal nerve of clitoris). Most of the neurons responding to the electrical search stimuli received a high degree of somatovisceral convergence, including inputs from the abdominal branches of the vagus, cervix, vagina, colon and skin territories on the perineum and trunk. Mean neuronal response thresholds for vaginal and cervical stimulation but not colon distention were significantly higher for animals tested during proestrus. Also, there was a shift in POA and BST neuronal responsiveness towards more inhibition and less excitation during proestrus for a variety of somatovisceral inputs. These data demonstrate that the changes in hormonal status affect the properties of POA and BST neurons, which likely relates not only to the functional importance of these inputs for reproductive behaviors but also for nociceptive processing as well.

Keywords: Preoptic area; Bed nucleus of stria terminalis; Pelvic nerve; Pudendal nerve; Reproductive organs; Cervix; Estrous cycle

Introduction

The location of CNS neurons responsive to stimulation of the female reproductive organs has been well documented throughout the neuraxis using a variety of different techniques, including neuroanatomical tracing, immunohistochemistry and electrophysiological studies. For example, single unit recordings indicate that many neurons receiving inputs from the female reproductive organs are found in the dorsal horn throughout the caudal extent of the spinal cord, from T13 through S2 segmental levels (Berkley et al., 1993b). Supraspinal regions containing neurons responsive to stimulation of these pelvic organs include the nucleus tractus solitarius, nucleus gracilis, and various subregions of the medullary reticular formation, thalamus and hypothalamus (see review by Hubscher, 2006a).

In our recent electrophysiological study of neurons in the medullary reticular formation, estradiol (but not progesterone)-associated response variations and a high degree of somatovisceral convergence was found (Hubscher, 2006b). The medullary reticular formation is one of several central regions known to be part of the circuitry mediating lordosis, a mating posture important for copulation and successful fertilization. Lordosis behavior has been studied extensively and involves both cutaneous stimulation of the flanks, rump and perineum as well as stimulation of the cervix and vagina during copulation. In addition, the full expression of lordosis has been shown to be hormonally mediated. Cutaneous aspects for the behavioral expression have been shown to be facilitated by the combination of estrogen and progesterone, while the pelvic organ components are facilitated only by estrogen (Castro-Vazquez and Carreno, 1985). Thus, extensive somatovisceral convergence and hormonal modulation, as seen at one level of the rostromedial medulla, is likely to be found throughout all levels

* Corresponding author. Fax: +1 502 852 6228.
E-mail address: chhubs01@louisville.edu (C.H. Hubscher).

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of the neuraxis where neuronal populations contributing to reproductive processes can be found.

In the present study, estrous cycle-related variations and degree of somatovisceral convergence was examined in the sexually dimorphic preoptic area (POA) of the hypothalamus and bed nucleus of the stria terminalis (BST), two estrogen-concentrating forebrain regions (Shughrue et al., 1997; Shughrue and Merchenthaler, 2001) known to play an important role in the neural control of the reproductive cycle, sexual behavior and mating (del Abril et al., 1987; Allen and Gorski, 1990). There is an extensive literature on male and female sexual behavior which covers a wide spectrum of studies, many of which focus on the POA and BST. For example, flank and perivaginal area stimulation in ovariectomized females receiving hormone treatments with estradiol benzoate and progesterone have shown that there is an increase of Fos like immunoreactivity in the POA and BST (Pfaus et al., 1993). Fos, the protein product of the immediate-early gene c-fos, is used by many labs as an endogenous marker to identify populations of neurons activated by a variety of sensory stimuli (Hunt et al., 1987; Dragunow and Faull, 1989; Curran and Morgan, 1995; Bialy and Kaczmarek, 1996). In mating studies, significantly more Fos immunoreactive cells are seen in the POA and BST in female rats when intromission occurs versus animals mounted by males but without any intromissions (Rowe and Erskine, 1993; Tetel et al., 1994). In addition, bilateral pelvic nerve transection reduces the number of Fos-IR cells activated by mating in the POA and BST regions (Erskine, 1993; Rowe and Erskine, 1993; Wersinger et al., 1993). Manual cervix stimulation has also been shown to increase the metabolic activity by 37% and 22% in the medial POA and BST region when compared to activity without stimulation (Allen et al., 1981). Manual vaginocervical stimulation with a probe is known to produce similar effects to those seen with intromission by males, which includes decreased locomotion, reversible analgesia, increased sperm transport and release of pituitary hormones (luteinizing hormone, oxytocin and prolactin) (Everett, 1967; Spies and Niswender, 1971; Crowley et al., 1976; Cruz et al., 1996; Pfaus et al., 1996).

Single unit extracellular recordings in rats were used in the present study to determine the response properties and degree of somatovisceral convergence of neurons in the POA and BST that respond to direct electrical pelvic and/or pudendal nerve stimulation. All neurons responsive to one or both of the nerve search stimuli were tested for responsiveness to stimulation of the abdominal branches of the vagus nerve, manual cervix stimulation with a probe, vaginal and colon distension with a latex

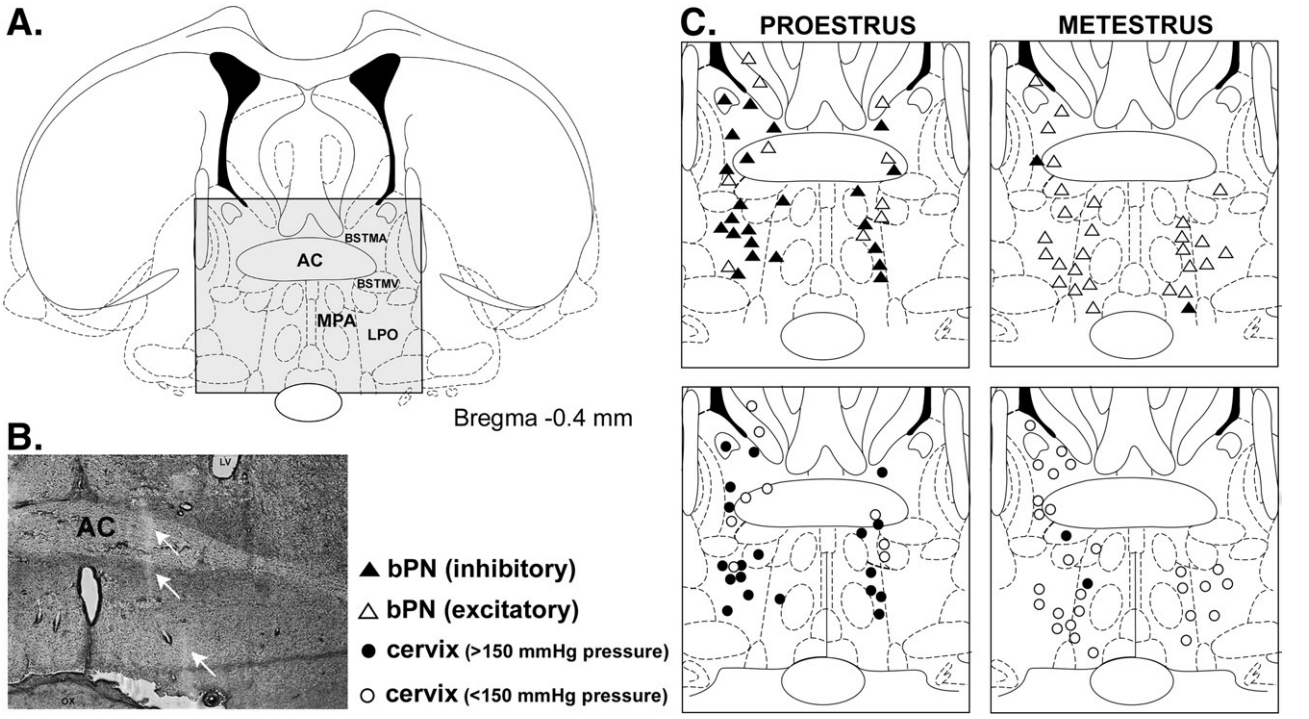

Fig. 1. Example showing the location of electrode tracks and neurons tested. Transverse section of the rat brain in A, adapted from Paxinos and Watson (1998), shows the search region (shaded region) at one level (−0.4 mm from bregma) through the POA of the hypothalamus and BST. In B (image at 200×), white arrows point out two electrode tracks (fluorescent dye bright in color version) through MPA used for histological reconstructions. The location of neurons at this one level (61 of 183) with responses to pelvic nerve (PN) stimulation is illustrated in C (top two boxes) with open and closed triangles. Note the contrast in excitatory (open triangles) versus inhibitory (closed triangles) responses with stage of estrous (few inhibitory neurons in metestrous, as shown in Table 1). Also note a similar contrast for cervix stimulation (C, bottom two boxes) for excitation/inhibition at higher (closed circles) and lower (open circles) response thresholds. Some of these neurons had mixed responses (complex neurons not indicated). Note that the atlas drawings provide only an estimation of the anatomical locations of the various structures. For example, the shape of the anterior commissure (AC) differs slightly in the actual section for the rat shown in B. Thus, the location of a few neurons, whose reconstruction is based upon surface depth, appear to be just within or bordering the anterior commissure (as shown in the closest atlas plate used in C); but in actuality, the neurons are within the target nuclei. AC — anterior commissure, bPN — bilateral pelvic nerve stimulation; BSTMA — Bed nucleus of stria terminalis, medial division, anterior; BSTMV — Bed nucleus of stria terminalis, medial division, ventral; LPO — lateral preoptic area, MPA — medial preoptic area, ox — optic chiasm.