Behavioural Brain Research 296 (2016) 431–441

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

Role of the dorsal diencephalic conduction system in the brain reward circuitry

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HIGHLIGHTS

- A Lesion at the DDC or MFB leads to significant attenuations in brain stimulation reward.
- Lesion effects are additive and depend on the current intensity used.
- The DDC contributes to the reward induced by both the DR and LH stimulation.
- Lesions are more effective in attenuating the reward induced by stimulation of the LH.

ARTICLE INFO

Article history:
Received 12 June 2015
Received in revised form 19 October 2015
Accepted 20 October 2015
Available online 26 October 2015

Keywords:
Dorsal raphe
Habenula
Lateral hypothalamus
Reward
Self-stimulation

ABSTRACT

Previous work with psychophysically based studies suggests that electrolytic lesion of the habenula, which lies in the dorsal diencephalic conduction system (DDC), degrades the intracranial self-stimulation (ICSS). This experiment was aimed at studying the importance of the DDC in brain stimulation reward, and its connections with other areas that support operant responding for brain stimulation. For this purpose, rats were implanted with stimulating electrodes at the dorsal raphe (DR) and lateral hypothalamus (LH), and lesioning electrodes in the medial forebrain bundle (MFB) and the DDC. Rats were trained to self-administer the stimulation at three different current intensities and were tested daily for changes in reward thresholds, defined as the pulse frequency required for half-maximal responding. The lesions were done at the DDC and the MFB, and were separated by two weeks interval during which the rats were tested for self-stimulation. At the end of the experiment, rats were transcardially perfused and their brains collected to determine the extent of the lesions and the locations of the stimulation sites. Results show that lesions at both the DDC and MFB produce larger and longer-lasting increases in the reward thresholds (upto 0.40 $\log_{10}$ units) than lesions at either pathway alone (upto 0.25 $\log_{10}$ units), and were more effective in attenuating the reward induced by the LH stimulation. These results suggest that there exist two parallel pathways, the MFB and the DDC, which could constitute a viable route for the reward signal triggered by ICSS.

1. Introduction

It is well established that electrical stimulation of certain brain areas such as the lateral hypothalamus (LH) and the dorsal raphe (DR) induces a rewarding effect that is strong enough to support operant responding in laboratory animals; rats will quickly learn to press a lever, for instance, to receive a short train of electrical pulses delivered to these regions [1,2]. Since its discovery more than 60 years ago, electrical self-stimulation has been extensively used in an attempt to characterize the neural substrates of appetitive behaviors. This animal model has the advantage of bypassing external sensory processes to directly excite the reward circuit of the brain, hence being less affected by variables inherent to these processes. Despite a large amount of research, our knowledge of the reward circuitry and its trajectory within the brain is still largely limited. The main issue in establishing a detailed map of the reward-relevant substrates has been the proper differentiation between the reward-relevant neural elements from other elements that do not play a role in the rewarding effect but are still activated by the electrical stimulation [3]. Studies that made use of psychophysical measures combined with behavioral collision techniques revealed unique anatomical and physiological prop-

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http://dx.doi.org/10.1016/j.bbr.2015.10.038
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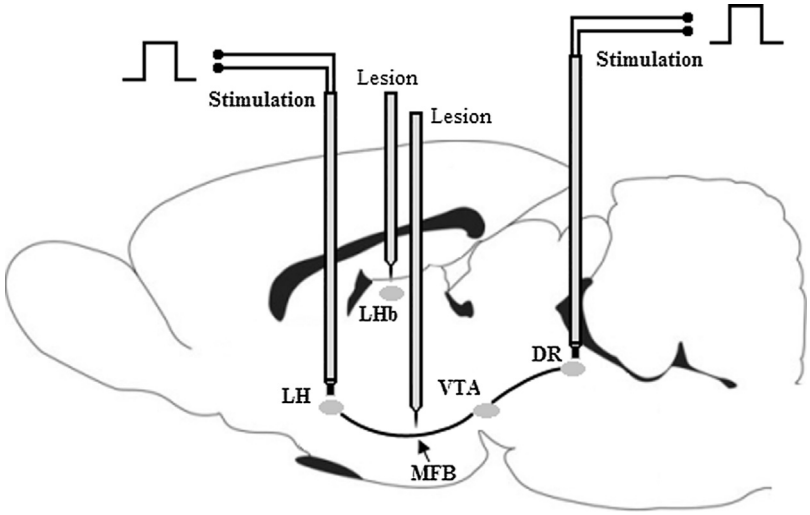

Fig. 1. Sagittal view of the rat's brain indicating the stimulation and lesion sites. Each rat was implanted with stimulation electrodes at the LH and DR, and lesion electrodes at the MFB and LHb, which is situated within the DDC.

erties of the reward-relevant neurons [3,4]. From these studies, we know that the reward signal initiated by electrical stimulation of the medial forebrain bundle (MFB) travels at moderate velocities (1–8 m/sec) along axons that possess short refractory periods (0.4–1.2 msec) and that link anterior regions of the LH to the ventral tegmental area (VTA) [3–5]. The hypothesis that the reward signal is carried by first-stage neurons traveling between regions anterior to the LH and the VTA led to the prediction that damage to the MFB should decrease the rewarding efficacy of LH and VTA electrical stimulation [6,7]. Consistently, sustained attenuations of LH [8–10] and VTA [11] self-stimulation threshold were observed following electrolytic lesions, or a knife cut, placed along the MFB. A common finding of these studies, however, is that in the great majority of cases, damage to the anterior MFB failed to attenuate the reward or induced a small transitory attenuation. These negative results were attributed to a highly diffuse neural network that contributes to reduce the probability of functionally disconnecting the pathway between the lesion and the stimulation sites (see [11]). A hypothesis to account for the large number of ineffective lesions is that the reward signal is carried by more than one pathway. Such hypothesis has been proposed by Murray and Shizgal [12] who used the behavioral version of the collision technique to reassess the physiological properties of the first-stage neurons that link the LH and the VTA. Using a high resolution frequency sampling, they observed collision intervals that were significantly longer than those reported in previous studies. Such long collision intervals imply that the first-stage neurons that they were stimulating had very slow conduction velocities (<1 m/s), a conclusion that was inconsistent with previous findings and with the duration of the refractory period. The discrepancy could be resolved assuming that the relevant neurons do not travel only within the MFB, the shortest course between the LH and the VTA, but also follow the course of the dorsal diencephalic conduction system (DDC), hence increasing the axonal length between the two stimulation sites.

The idea that diencephalic structures are involved in brain stimulation reward comes from early lesions studies showing that rats are still able to self-stimulate at the LH after surgical removal of telencephalic structures [13,14], and following 6-OHDA injection into the substantia nigra [15]. Not only do these studies suggest that the reinforcing mechanisms of ICSS are independent of dopamine transmission, they also propose the existence of a diencephalic locus of integration of reward [16]. The DDC has recently received a lot of attention because electrical stimulation along its trajectory is effectively rewarding, suggesting that it likely contains reward-relevant axons [17,18]. This pathway links structures that serve as a key relay between the forebrain and several mid- and hindbrain sites, and that play an important role in the regulation of reward-seeking behaviors [19–22]. It has been shown that in response to rewarding stimulation, sites along the DDC increase the expression of the neuronal marker Fos [23,24]. Moreover, the DDC receives information through the stria medullaris (sm) from the anterior portion of the MFB, and has efferent projections terminating in the caudal mesencephalon [20]. Many of the fibers within this pathway synapse in important regions that support self-stimulation, such as the lateral habenula (LHb) [2,19]. The LHb, which is located centrally along the DDC, receives dopaminergic innervations that arises primarily from the medial VTA [25–27], a region that also innervates key structures involved in reward such as the ventral striatum [28]. The hypothesis that the DDC plays an important role in brain stimulation reward is further supported by a previous study by Morissette and Boye [2], who reported sustained attenuations of the rewarding effectiveness of the median raphe, DR, LH and VTA stimulation in more than 25% of tested rats following electrolytic lesions of the habenula. This reinforces the hypothesis that reward-relevant neurons that link mesencephalic and rostral diencephalic regions likely travel through the DDC. The present study was aimed at testing this hypothesis. We trained rats to self-administer electrical stimulation at the level of the DR and the LH; then we made a small lesion at the DDC followed two weeks later by a second lesion at the MFB (and vice versa). Using the curve-shift paradigm, reward thresholds were measured daily for 2 weeks after each lesion at three different current intensities and for each stimulation site. Results show that the DDC and MFB lesions tend to shift the reward threshold towards higher values, suggesting that these pathways play an important role in brain stimulation reward.

2. Material and methods

2.1. Subjects

Adult male Long Evans rats, purchased from Charles River Canada, served as experimental subjects. The animals were kept in a temperature (22 °C) and humidity (50%) controlled animal colony lit from 6:30 am to 6:30 pm. They were individually housed in a standard cage with unrestricted access to food and water, and were allowed to habituate to the animal colony for at least 5 days prior