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Serotonergic fibers distribution in the midline and intralaminar thalamic nuclei in the rock cavy (*Kerodon rupestris*)

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ABSTRACT

The thalamic midline/intralaminar complex is part of the higher-order thalamus, which receives little sensory input, and instead forms extensive cortico-thalamo-cortical pathways. The midline thalamic nuclei connect with the medial prefrontal cortex and the medial temporal lobe. On the other hand, the intralaminar nuclei connect with the fronto-parietal cortex. Taking into account this connectivity pattern, it is not surprising that the midline/intralaminar complex has been implicated in a broad variety of cognitive functions, including memory process, attention and orientation, and also reward-based behavior. Serotonin (5-HT) is a neurotransmitter that exerts different post-synaptic roles. Serotonergic neurons are almost entirely restricted to the raphe nuclei and the 5-HT fibers are distributed widely

Abbreviations: 3V, 3rd ventricle; 5-HT, serotonin; 5-HT-IR, 5-HT immunoreactive fibers; AD, anterodorsal thalamic nucleus; AM, anteromedial thalamic nucleus; AOI, area of interest; CL, centrolateral thalamic nucleus; CM, central medial thalamic nucleus; DAB, diaminobenzidine; f, fornix; fr, fasciculus retroflexus; Hb, habenular nucleus; IAD, interanterodorsal thalamic nucleus; IAM, interanteromedial thalamic nucleus; IMD, intermediodorsal thalamic nucleus; MD, mediodorsal thalamic nucleus; mt, mammillothalamic tract; PC, paracentral thalamic nucleus; PF, parafascicular thalamic nucleus; PT, paratenial thalamic nucleus; PV, paraventricular thalamic nucleus; PVA, paraventricular thalamic nucleus, anterior part; PVP, paraventricular thalamic nucleus, posterior part; Re, reuniens thalamic nucleus; Rh, rhomboid thalamic nucleus; ROD, relative optical density; sm, stria medullaris of the thalamus; Sub, submedius thalamic nucleus; VRe, ventral renuens thalamic nucleus; ZI, zona incerta

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Optical density
Fiber morphology

throughout the brain, including the midline/intralaminar complex. The present study comprises a detailed description of the morphologic features and semiquantitative analysis of 5-HT fibers distribution in the midline/intralaminar complex in the rock cavy, a typical rodent of the Northeast region of Brazil, which has been used by our group as an anatomical model to expand the comprehension about phylogeny on the nervous system. The 5-HT fibers in the midline/intralaminar nuclei of the rock cavy were classified into three distinct categories: (1) beaded fibers, which are relatively fine and endowed with large varicosities; (2) fine fibers, with thin axons and small varicosities uniformly distributed in whole axon; and (3) stem axons, showing thick non-varicose axons. Moreover, the density of 5-HT fibers is variable among the analyzed nuclei. On the basis of this diversity of the morphological fibers and the differential profile of optical density among the midline/intralaminar nuclei of the rock cavy, we conclude that the serotonergic system uses a diverse morphologic apparatus to exert a large functional repertory in the midline/intralaminar thalamic nuclei.

1. Introduction

The rock cavy (*Kerodon rupestris*), a typical rodent in the Northeast region of Brazil, dwells in the mountainous regions of the Caatinga in the Brazilian semi-arid interior. Morphological (Silva Neto, 2000) and molecular biology studies (Rowe and Honeycutt, 2002) put the genus Kerodon in the family Hydrochaeridae, in which the capybara (*Hydrochoerus hydrochaeris*) is also included. The rock cavy has a crepuscular habit (Sousa and Menezes, 2006) and has been used in several neuroanatomical studies in our laboratory (Cavalcante et al., 2008; Nascimento et al., 2008, 2010a, 2010b; Soares et al., 2012). The rock cavy has advanced our understanding about the nervous system, providing a framework for the interpretation of evolutionary patterns, allowing inferences to be drawn about the brain and its phylogenetic congruence among diverse biological features.

The structural organization of the raphe has been extensively studied in various species (Azmitia and Gannon, 1983; Dahlstrom and Fuxe, 1964; Dwarika et al., 2008; Fuxe et al., 1969; Harding et al., 2004; Hornung and Fritschy, 1988; Hornung, 2010; Limacher et al., 2008; Moon et al., 2007; Paxinos and Watson, 2007). The nuclear organization of the raphe serotonergic system in the rock cavy is similar to that described in other mammals with small anatomical variations (Soares et al., 2012). Moreover, subsequent reports using tracing techniques have pointed out the dorsal and median raphe nuclei as the main sources of serotonergic projections (Azmitia and Segal, 1978; Moore et al., 1978; Morin and Meyer-Bernstein, 1999; Vertes and Martin, 1988; Vertes, 1991; Vertes et al., 1999), although the majority of the serotonergic fibers are concentrated in limbic regions of the forebrain (Jacobs and Azmitia, 1992; Lowry et al., 2008; Steinbusch, 1981; Vertes and Linley, 2007, 2008). Serotonin (5-HT) exerts excitatory modulatory activity on some of its targets (Curtis and Davis, 1962; Kayama et al., 1989; Marks et al., 1987; Monckton and McCormick, 2001; Rogawski and Aghajanian, 1980; Yoshida et al., 1984). In other areas, however, it produces changes in the conductance and permeability of cell membranes, causing hyperpolarization of neurons (Mccormick and Pape, 1990; Lee and Mccormick, 1996). The functional duality of the 5-HT in the thalamus has been widely associated with the various types of receptors present in the different thalamic nuclei (Chapin and Andrade, 2001a, b; Lopez-Gimenez et al., 1998, 2001; Kia et al., 1996; Mengod et al., 1996; Pompeiano et al., 1994), as well as in differences in fibers morphology, origin, and preference in area of innervation (Wilson, 1989). The 5-HT axons are generally divided into three morphological different fiber types. Thin axons with small fusiform or granular boutons, named fine fibers, are supposed to originated from the dorsal raphe nucleus; the beaded fibers with large spherical boutons; and non-varicose stem-axons originated from the beaded fibers, supposed to originated from the median raphe nucleus (Hornung and Fritschy, 1990; Wilson and Molliver, 1991).

A low-frequency stimulation of the midline/intralaminar thalamic nuclei induces a low synchronous activity in different regions of the cortex (Dempsey and Morison, 1943). This thalamic nuclear complex is classically viewed as nonspecific thalamus, exerting a global influence on the cortical layers (Groenewegen and Berendse, 1994). Nowadays, the notion of the nonspecific functions has been changed as a result of several anatomical studies which have demonstrated, that the midline/intralaminar complex projects to specific areas of the cerebral cortex, mainly to the prefrontal cortex (Groenewegen and Witter, 2004; Van der Werf et al., 2002; Vertes, 2006). Furthermore, the electrical stimulation of individual nuclei produces selective effects on their cortical targets (Viana di Prisco and Vertes, 2006). Descriptions of the serotonergic projections in the thalamus have been shown in monkey and rat studies (Cropper et al., 1984; Lavoie and Parent, 1991; Vertes, 2002; Vertes et al., 2010) and suggest that the serotonergic fibers exert a fundamental role on modulation in the midline/intralaminar thalamic nuclei. Furthermore, it is widely agreed that cell types and morphological fiber pattern serve as the building blocks of nervous systems and that exploring their diversity and determining how cells are assembled into circuits is essential for understanding brain function.

In the present study we aim describe and compare the distribution of serotonergic fibers in the rock cavy midline/intralaminar thalamic nuclei. We also assess the relative abundance of serotonergic fibers throughout the various