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Comparison of projections of the dorsal and median raphe nuclei, with some functional considerations

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Abstract. It is well established that the brainstem contains discrete groups of serotonin-containing neurons with extensive axonal processes that distribute throughout the neuroaxis. Serotonergic neurons have been implicated in a range of functions including sleep/wakefulness, feeding, affect/emotion, thermoregulation, and cognitive behaviors. We describe the projections and some functional properties of the two major serotonergic cell groups of the brain, the dorsal raphe (DR) and the median raphe (MR) nuclei. DR fibers distribute widely throughout the forebrain to dopamine-containing nuclei of the ventral midbrain, the lateral hypothalamus, the midline thalamus, amygdala, the dorsal and ventral striatum and adjoining regions of the basal forebrain, and most of the cortex. By contrast with DR, MR is a midline/paramidline system of projections. Specifically, MR fibers mainly distribute to forebrain structures lying on or close to the midline including the medial mammillary and supramammillary nuclei, posterior and perifornical nuclei of the hypothalamus, midline and intralaminar nuclei of the thalamus, lateral habenula, medial zona incerta, diagonal band nuclei, septum and hippocampus. Overall, MR projections to the cortex are light. With few exceptions, DR and MR project to separate, non-overlapping regions of the forebrain — or, in effect, DR and MR share the serotonergic innervation of the forebrain. We discuss roles for DR in sleep/wake control, feeding/appetite and mood/affect, and for MR in the control of electroencephalographic (EEG) activity of the hippocampus — or states of hippocampal EEG desynchronization.

Keywords: Septum; Hippocampus; Midline thalamus; Theta rhythm; Emotion; Depression

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1. Introduction

It is well established that the brainstem contains discrete groups of serotonin-containing (5-hydroxytryptamine, 5-HT) neurons, extending from the caudal medulla to the rostral midbrain. It is equally well documented that the axonal processes of these cells are extensive, distributing to structures throughout the neuroaxis. As would be expected from this widespread distribution and influence, 5-HT cells participate in a range of functions including sleep/wakefulness, feeding, affect/emotion, thermoregulation, motivation and cognitive behaviors [1].

In their original report, Dahlstrom and Fuxe [2] identified in the rat nine serotonin-containing cell groups of the brainstem which they termed B1–B9. With the exception of B9, these 5-HT-containing nuclei were located on the midline, and as such, were designated raphe nuclei; *raphe* meaning seam, or in this context, the line of junction (midline) of the two halves of the brainstem. Possibly excluding B9, the alpha-numerical designations for the raphe nuclei have been replaced by names which reflect their anatomical location or characteristics as follows: B1, raphe pallidus; B2, raphe obscurus; B3, raphe magnus; B5, raphe pontis; B7, dorsal raphe nucleus (DR); and B8, median raphe nucleus [3,4].

In addition to these raphe groups, newer histochemical procedures [5,6] have revealed the presence of relatively significant numbers of 5-HT neurons off (lateral to) the midline within the medulla and pons/midbrain. Those of the medulla primarily extend laterally from the nucleus raphe magnus ventrally within the rostral medulla, while 5-HT cells of the pons/midbrain (outside of B9) stretch laterally from DR across the dorsal pontine tegmentum as well as diffusely populate the pontomesencephalic reticular formation (RF) [6]. For the most part, caudal raphe nuclei (B1, B2, B3) give rise to descending projections to the lower brainstem and spinal cord, while rostral raphe nuclei, particularly DR and MR, project widely throughout the upper brainstem and forebrain [1,7–11].

The present review focuses on DR and MR, with some consideration of the supralemniscal (SLN) nucleus (B9). We describe: (1) general characteristics of 5-HT cells in DR, MR and SLN; (2) projections of DR and MR; and (3) some functional properties of DR and a role for MR in modulating states of the hippocampal EEG.

2. Serotonergic neurons of MR, DR, SLN and the pontomesencephalic reticular formation (PMRF)

2.1. DR and MR

As is well recognized, the dorsal and median raphe are densely populated with serotonergic neurons—DR more so than MR. At the midbrain, 5-HT cells of DR are fairly concentrated along the midline, whereas further caudally they remain densely packed medially, but also extend laterally from the core of DR to its lateral ‘wings’ (Fig. 1). Serotonergic cells of DR are typically large (30–40 μm), fusiform in shape, stain darkly for 5-HT and contain about 4–5 primary dendrites radiating from the cell body.

By comparison with DR, there are considerably fewer 5-HT-containing neurons in MR. As shown in Fig. 1, serotonergic MR cells disperse fairly widely throughout the nucleus. Those located dorsally in MR are predominantly small (10–12 μm), oval, and stain lightly