Nuclei of the human raphe

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Summary: Along the raphe of the brain stem, a series of small neuronal groups can be observed in the medulla oblongata, the pons and the mesencephalon. The neurons located in and adjacent to the raphe are considered to produce mainly serotonin (5-HT). The groups of nuclei containing 5-HT were first reported in experimental animals in the early 1960s¹. The presence of such nuclei, however, has not yet been brought to light in the human brainstem except the few atlases²,³, although in several neuroanatomy textbooks⁴, extrapolated data are shown in the form of drawings as if they were the data from the human brain. The aim of this study is to present microscopic photos of such raphe nuclei made from serial sections of the human brainstem, and to clarify the differences between findings in human and textbook drawings from animal data.

Researches on the raphe nuclei has been reported in experimental animals since the early 1900s⁵. However, in the human brainstem, such group nuclei have not yet been studied precisely. We made serial sections of the human brainstem and cerebellum to present precise findings of the raphe group nuclei.

Material and Methods

We used the brain stem and cerebellum from a 63-year-old Japanese female cadaver. The cause of death had no direct or indirect connection with the central or peripheral nervous system, and no gross pathological alterations were observed. We injected 12% formaldehyde solution into the femoral artery prior to removing the whole brain the next day. After further fixation in 3.7% formaldehyde solution for one week, we cut the brainstem and cerebellum as one block, and immersed the block into secondary chromic acid fixative⁶ for two weeks at room temperature. Then we renewed the fixative to continue the immersion another week at 37°C in an incubator. The block was washed using a pipette washer with siphon mechanism, and was dehydrated in a series of graded alcohol and followed by embedding in celloidine (nitrocellulose). The celloidine block was sliced at 40 μm thickness to make complete serial transverse sections. Then we stained every 5th section alternatively with Kultschitzky and K-B methods. Details of the staining methods have been given in previous reports⁶.

Results

According to our careful observations of the serial brainstem sections, the following groups of raphe nuclei can be recognized: (1) nucleus linealis oralis, (2) nucleus linealis intermedius, (3) nucleus raphe medialis, (4) nucleus supratrochlealis (or nucleus raphe dorsalis), (5) nucleus raphe pontis, (6) nucleus centralis superior medialis, (7) nucleus centralis superior dorsalis, (8) nucleus raphe magnus, (9) nucleus raphe pallidus, (10) nucleus raphe obscurus intraraphalis, and (11) nucleus raphe obscursus extraraphalis.

Locations of the Nuclei and Neuronal Findings

Precise nuclear locations and their neuronal findings are described below.
(1) *nucleus linealis oralis* (Plate I)
This nucleus is located between both sides of the nucleus ruber at the upper level of the mesencephalon. The included neurons are quite small in number, and the neuronal soma sizes are around 20 μm in diameter.

(2) *nucleus linealis intermedius* (Plate I)
This nucleus is located caudally to the nucleus linealis oralis at the caudal level of the mesencephalon. The neurons are packed together and are in larger numbers compared to the nucleus linealis oralis. The soma sizes of included neurons are around 20–30 μm.

(3) *nucleus raphe medialis* (Plate II)
This nucleus is located among the nerve fibers of the decussatio pedunculorum cerebellarum superiorum. The somata of the neurons are 30 μm in diameter and are scattered among the fibers.

(4) *nucleus supratrochlealis (equivalent to nucleus raphe dorsalis in animals)* (Plate II)
This nucleus occupies the ventral part of substantia grisea centralis which begins at the same level of the nucleus nervi trochlealis toward the oral direction. The included neurons are aggregated together, and are the largest in number among the raphe group. The soma sizes of neurons measure 30–40 μm in diameter.

(5) *nucleus raphe pontis* (Plate II)
This nucleus can be observed between the decussatio pedunculorum cerebellarum superiorum and the fasciculus longitudinalis medialis. The included neurons are packed together, forming a small mass. The soma sizes of neurons are 20–40 μm in diameter.

(6) *nucleus centralis superior medialis* (Plate III)
The location of this nucleus is evident, even under the myelin sheath stain, along the raphe at the upper level of the pons. The included neuronal somata are around 30 μm in diameter.

(7) *nucleus centralis superior dorsalis* (Plate III)
This nucleus is located near the fourth ventricle at the same level as the nucleus centralis superior medialis. The soma sizes of neurons measure 20–40 μm in diameter.

(8) *nucleus raphe magnus* (Plate III)
This nucleus can be observed at the middle level of the pons (the same level as the abducent nucleus). The included neuronal somata measure 30–60 μm in diameter. This nucleus contains large size neurons which are scattered in the nucleus, as the name “magnus” indicates.

(9) *nucleus raphe pallidus* (Plate IV)
This nucleus is located between both sides of lemniscus medialis at the lowest level of the pons. The soma sizes of neurons vary from 20–60 μm in diameter. This nucleus contains various sizes of neuronal somata.

(10) *nucleus raphe obscurus intraraphalis* (Plate IV)
The location of this nucleus in the raphe is uncertain. The neurons are very small in number, however, and their soma sizes are 40–50 μm in diameter.

(11) *nucleus raphe obscurus extraraphalis* (Plate IV)
This nucleus is attached to the raphe, forming a small mass, but its location is also uncertain. The neuronal soma sizes are the smallest in the raphe groups and measure 10–20 μm in diameter.

Discussion

The idea of the grouping of raphe nuclei first came from the ordinary staining method used in rabbit brains5. However, it took more than half a century to discover that neurons containing serotonin were found not only in the raphe nuclei, but also in the surrounding area and the substantia grisea centralis5. Some authors considered the raphe group nuclei to be phylogenetically old7. The raphe nuclear group in humans has been described by several authors2,3,8. Although the midsagittal projection of the raphe nuclear group in the human brainstem is fairly small in size and of elongated shape, except for the nucleus supratrochlearis (or nucleus raphe dorsalis in animals, fig. 1), midsagittal drawings of raphe nuclear groups shown in textbooks are represented as being larger and not elongated (fig. 2, cat4). These differences might be derived from differences between humans and animals. In animals, raphe group nuclei can be divided into two groups: oral and caudal. In humans, however, this classification remains undecided4. Generally speaking, in animals the caudal groups include the nucleus raphe obscurus, the nucleus raphe pallidus and the nucleus raphe magnus, while the oral groups include the nucleus raphe pontis, the nucleus raphe centralis superior, the nucleus raphe dorsalis and the nucleus raphe linearis9. The caudal groups are considered to project to spinal levels, while the oral groups are considered to have extensive projections to various nuclei in the brainstem. Projections to diencephalic structures are most numerous from the nuclei raphe medialis et dorsalis and from the nucleus raphe pontis. The nucleus raphe medialis and the nucleus raphe dorsalis also project widely to telencephalic structures5. Even though in human raphe group nuclei, the nucleus supratrochlearis (which corresponds to nucleus raphe dorsalis in animals) consists of a very large number of neurons compared to the other nuclei, such appearance is not contradictory to the developmental enlargement of the human telencephalon. To elicit proof of neuronal connections in humans, it is indispensable to precisely examine postmortem brains with various types of lesions, for example cerebrovascular diseases, cerebral neoplasms, degenerative diseases, or simple aging, etc. in order to examine the precise sites of lesions, and also to examine secondary degenerative changes of raphe group nuclei with serial brainstem sections. However, these projections have not yet been confirmed in human raphe nuclei at present.
Fig. 1. Localization of human raphe nuclei.

Fig. 2. Midsagittal drawing of the brainstem indicating the positions of the raphe nuclei (cat, Parent, 1996)
- project to the diencephalon and telencephalon
- project to the spinal cord
References


ABBREVIATIONS for Plates


Staining methods: Kultschitzky’s myelin sheath stain (scale bar = 10 mm) Klüver-Barrera’s method
Explanation of Figures

Plate I

1. Nucleus linealis oralis
2. Nucleus linealis intermedius
3. Nucleus raphe medialis
4. Nucleus supratrochlearis (= Nucleus raphe dorsalis)
5. Nucleus raphe pontis
Plate III

6. Nucleus centralis superior medialis
7. Nucleus centralis superior dorsalis
8. Nucleus raphe magnus
Plate IV

9. Nucleus raphe pallidus
10. Nucleus raphe obscurus intraraphalis
11. Nucleus raphe obscurus extraraphalis