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EFFERENT CONNECTIONS OF THE PERIAQUEDUCTAL GRAY MATTER IN THE CAT

by

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Efferent Connections of the Periaqueductal Gray Matter in the Cat

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CHAPTER I

INTRODUCTION

The mesencephalic periaqueductal gray matter is mentioned in such a short and perfunctory manner in the majority of neuroanatomical text books to suggest that it is an area of little significance. Within the last decade, however, a number of physiological studies have shown this region to be an important link in the transmission of impulses from diencephalic centers to the lower brain stem, and even the spinal cord. Surprisingly, these observations prompted little anatomical investigation of the region or its fiber connections. Often the anatomical work done, was the byproduct of a major study of a related area, usually the hypothalamus or the reticular formation. The unanswered need for an organized and systematic investigation of the efferent and afferent connections of the region prompted this study.

The most effective method of tracing efferent fiber connections in the central nervous system is to make lesions in the area of interest in an experimental animal and keep it alive for an appropriate length of time to allow for degeneration of the affected axons. Then, the animal is sacrificed and the brain tissue stained by a method based on silver impregnation of the degenerating axons and terminal boutons.

Accordingly, lesions were stereotaxically placed in the periaqueductal gray matter in a number of cats and their brains were subsequently prepared histologically and stained to allow the investigator to trace the resulting degeneration.

The author reviewed the literature on the anatomy of the region, and prepared a small series of normal animals for histological examina-

tion. This resulted in an increased understanding of the cytoarchitecture of the region and provided a set of slides of normal tissue for comparison with lesioned tissue.

Subsequent chapters describe the materials and methods, and results of the above study. These experimental results and observations gleaned from the review of pertinent literature were then compared and discussed.

Although much work is yet to be done on the central gray matter and its fiber connections, this study is intended as another step forward to an ultimately full understanding of the periaqueductal gray matter's role in the overall function of the central nervous system.

CHAPTER II

ANATOMICAL CONSIDERATIONS

According to text books of vertebrate embryology, including the human, the mesencephalon is bound dorsally by the posterior commissure and ventrally by the mammillary bodies to form its rostral border, and caudally by the isthmus. The midbrain undergoes fewer changes than the forebrain or the hindbrain and tends to be hidden by them as they develop. At this level the alar plate, the basal plate and the roof plate are still present although the floor plate has terminated. The roof plate loses its identity at two months leaving only the alar plate and the basal plate divided by the sulcus limitans. After the third month of development the primitive neural cavity narrows to become the cerebral aqueduct according to most texts. This narrowing is a point of active disagreement among different authors. Most report that it is a case of both relative and absolute narrowing, but Minot (74) believed that there was growth, with a little enlargement of its cavity, making the cavity appear relatively smaller. The present author took measurements from several sets of slides available in a human embryonic collection, and on the basis of this data, concluded that there is no actual change in size of the cerebral aqueduct, and that the apparant narrowing of the aqueduct is a result of growth of the surrounding tissue.

The mesencephalon is divided into alar and basal plates by the sulcus limitans. The basal plate develops first, as it does throughout the brain, and forms the ventral portion or the tegmentum. Later, the

alar plate develops demarcating the tectal portion of the midbrain. According to Castaldi, (22) the periaqueductal gray matter is similarly divided, and the dorsal portion of the gray develops from the alar plate along with the tectum, and the basal plate gives rise to the ventral portion. He also points out that the ventral portion develops before the alar or dorsal. Simpkins (100) on the other hand, states that all parts of the central gray have a common origin from the alar plates.

With the exception of the ventral portion of the periaqueductal gray matter, where several nuclear structures are readily discernable, the main body of the gray does not readily lend itself to nuclear differentiation. However a review of the available literature reveals that many authors have identified and named numerous nuclei within this structure.

In 1923 Castaldi (22) reviewed the literature on these nuclear configurations and proposed a simplified system of nomenclature to reduce the multiplicity of different names given cell groups by earlier authors. His system was based upon the predominance of a given cell (type and size) in a particular area, using the guinea pig as the experimental animal. Accordingly, the whole ventral area of the central gray mass was named the ventral nucleus and it was sub-divided into four basic parts: the two unpaired "partes medianas"; and the two bilateral "partes laterales". The "parte mediana" was subdivided into a dorsal portion and a smaller ventral one. The dorsal included all nuclei, as previously designated in the literature. Thus, the nucleus of the dorsal raphé (3), the nucleus of the idem tegmenti (119), and Cajal's (89)

central magnocellular nucleus of the raphé were all included in this portion. The smaller ventral portion included the nucleus angustus (120), the posterior nucleus of the raphé (119) and the inferior cells of the raphé (89).

Each "parte laterale" included numerous previously designated nuclei such as Marburg's (69) dorsal tegmental nucleus, the posterior or accessory trochlear nucleus (120), the internal cellular matter (89) the nucleus of the lateral aqueduct (125), and the parvicellular nucleus of Ziehen (124).

Although previous authors had designated numerous dorsal nuclei of the central gray matter, Castaldi divided it into only three nuclei, the single unpaired mediodorsal nucleus and the bilateral latero-dorsal nuclei.

In 1933, Sheehan (99) described the nuclear structure of the peri-aqueductal gray matter of several species, including man. According to his observations, the central gray matter was defined as the region bounded by the decussation of the trochlear nerves caudally and the posterior commissure rostrally. He divided this structure into four linear subdivisions: 1. the retrotrochlear area; 2. an area around the trochlear nucleus; 3. an area around the oculomotor complex; and 4. an area on the anterior end near the posterior commissure. In the two most caudal regions, the retrotrochlear area and the trochlear area, he described a nucleus extending from the region of the dorsal tegmental nucleus to the oculomotor nucleus. He called this nucleus the "fountain like" nucleus due to its general configuration. Caudally it fused with the dorsal tegmental nucleus and as it passed rostrally through the retrotrochlear region it spread laterally from its median

position. Upon reaching the trochlear region the cells began to fade until only a few cells existed at the level of the oculomotor complex. Within the trochlear region, he defined yet another nuclear group bilaterally and named this the dorsolateral nucleus. The remainder of the central gray matter in this region was occupied by a group of smaller cells called the nucleus parvicellularis by Ziehen (124). Sheehan agreed with Castaldi's description of the rostral portion of the periaqueductal gray matter.

In 1943 the University of Michigan's Laboratory of Comparative Neurology authored an extensive study on the nuclear configuration of the mammalian midbrain. (15, 30, 31, 32, 33, 34, 35, 41, 42, 112, 122) In one section of this study, Brown (15) dealt with the midbrain of the dog and cat exclusively and stated that the mesencephalic gray matter should be divided into dorsal, lateral and ventral portions. The pars dorsalis extending caudally from the area of the posterior commissure to the inferior colliculus becomes continuous with the chief nucleus. He also considered this area to be part of the periventricular layer of the optic tectum of the superior colliculus. Within the pars ventralis he included the following nuclear structures: the oculomotor complex; the nucleus of Darkschewitch; the dorsal nucleus of the raphé; the laterodorsal tegmental nucleus; and the dorsal tegmental nucleus. Lying on either side of the central gray matter and connecting the dorsal and ventral portions was the pars lateralis. Only one nuclear mass, the dorsal nucleus of the posterior commissure, was said to develop within this lateral area.

The other mammals investigated in this study showed some minor variations, but on the whole, the nuclear configuration of the

periaqueductal gray was found to hold throughout the many species.

In 1954 Olszewski and Baxter (85) in their human atlas took a radically new approach to the organization of the central gray matter. Instead of the traditional division of the central gray into dorsal and ventral components, they proposed a nomenclature based on a concentric arrangement of cells. They described the griseum centrale mesencephali as a mantle of cells enveloping the dorsal and lateral aspects of the cerebral aqueduct in the caudal half of the mesencephalon and completely surrounding the aqueduct in the rostral half. The ventral portion of the caudal half consisted of the nucleus supratrochlearis which extended from the caudal level of the inferior colliculus to the caudal pole of the oculomotor complex. Based on variation of cell type and the density of distribution, three subnuclei were identified within the griseum centrale mesencephali. The first, the griseum centralis mesencephali medialis, was the innermost region of the central gray matter which lay adjacent to the cerebral aqueduct. This area was formed by small, elongated, darkly staining cells that are sparsely distributed. The second division, the griseum centralis mesencephali lateralis, is located dorsal and lateral to the subnucleus medialis and forms the outermost portion of the central gray matter. It includes densely distributed small to medium sized fusiform or triangular cells which stain with medium intensity. They named the third subnuclei the griseum centralis mesencephali dorsalis, and described it as a small, oval shaped cell group immediately dorsal to the cerebral aqueduct in the rostral half of the mesencephalon. It lay dorsal to the subnucleus lateralis and on each side touched the subnucleus medialis. It is composed of many glial cells, among which a few small elongated darkly

stained neurons can be found.

Olszewski and Baxter stated that the large unpaired nucleus of the ventrocaudal area of the central gray matter, the supratrochlear nucleus, was roughly the same as Meynert's "fountain nucleus" (120), being composed of a central portion with two lateral wings. The central portion lay between the medial longitudinal fasciculi and extended up to the cerebral aqueduct. The lateral wings passed dorsally over the medial longitudinal fasciculi and the trochlear nuclei. This nucleus was composed of plump oval or fusiform, darkly stained cells with eccentric nuclei, and with the Nissl substance clumped around the walls of the cells.

Little additional work was done on the cytoarchitecture of the mesencephalon until Taber (111) published a paper on the subject in 1961. This study divided the periaqueductal gray matter into three basic portions, as had been done by many earlier authors. This division was based on topographical and cytological characteristics and the regions were defined as the dorsal, lateral, and ventral regions. The dorsal region ran from the rostral inferior collicular level to the posterior commissure. The lateral region extended from the anterior medullary velum to the mesencephalic-diencephalic junction. The ventral region extended from the junction of the pons and mesencephalon rostral to the diencephalon.

Taber described the central gray matter as a structure composed of medium and small sized oval or fusiform shaped cells with eccentric nuclei and moderately stained cytoplasm. The dorsal area characteristically contained a great number of glial cells. The lateral region was markedly cellular while the ventral region contains sparsely dis-

tributed small cells. The photomicrographs used to illustrate the three regions of the periaqueductal gray were of too low a magnification to make cell recognition possible. Using a criterion of cell density alone, her division of the central gray into areas appears to this author to be very arbitrary.

Snider and Neimer's atlas (110) on the brain stem of the cat was published in 1961 also. As in most atlases, the central gray matter was not divided into regions or subnuclei. The large photomicrographs of the Nissl stained sections demonstrated the differences in the cell density of each area although the actual cell type or size could not be determined.

The latest study of the brain stem of the cat was done by Berman (11) and while it is basically a cytoarchitectonic atlas, it also includes stereotaxic co-ordinates. While he described the periaqueductal gray matter as containing an inner cell-sparce zone surrounded by the outer cell-rich zone throughout its longitudinal extend, he did not adopt the Olszewski and Baxter nomenclature and divisions. Instead, he distinguished four subdivisions: mediolateral; laterodorsal; ventral; and lateroventral. These subdivisions are very similar to Castaldi's (22).

Berman (11) also distinguished several distinct nuclear masses partially embedded within the borders of the central gray substance. One such mass was the nucleus incertus, or nucleus of Streeter, which lay dorsal to the medial longitudinal fasciculus, and just medial to the dorsal tegmental nucleus at the level of the isthmus. It was included the ventral subdivision of the central gray as was the dorsal nucleus of the raphé. Between the ventral and the lateroventral subdivisions

lay the dorsal tegmental nucleus. Rostral to these nuclei, and the only nuclear mass to be wholly embedded in the central gray substance, was the nucleus of Darkschewitch. This small nucleus was in the ventrolateral portion of the periaqueductal gray matter.

At the level of the posterior commissure was a small area of the central gray separate from the main mass and lying between the commissure of the superior colliculus and the posterior commissure. This was called the intracommissural nucleus by Brown (15), but because the cellular make-up of this small area was the same as that of the central gray matter, Berman (11) did not consider it a separate subdivision.

The major fiber tract associated with the periaqueductal gray matter is the dorsal longitudinal fasciculus of Schütz, or by other terminologies, the fasciculus periependymalis (16, 17, 18, 29, 35, 59, 89, 114), the periventricular system of Gurdjian (47, 48), and the posterior longitudinal fasciculus (8, 10). Gurdjian used the name dorsal longitudinal fasciculus only for that portion of the system which arose from and extended caudal to the dorsal tegmental nucleus. Text books (28, 91, 115) state that dorsal longitudinal fasciculus is a bundle of thinly medullated or unmedullated fibers which interconnect the preoptic area and the hypothalamus with brain stem nuclei. It runs through the ventrolateral area of the periaqueductal gray matter throughout the midbrain and gives off fibers to the superior colliculus. It contains fibers from the anterior, paraventricular, dorsal and posterior hypothalamus and has ascending and descending fibers connecting the central gray substance at different levels. Kuhlenbeck (62) observed a pretectohypothalamic component in the rabbit (62) theorized that it was probably present in man

(60, 61).

Several authors (47, 59, 114) pointed out that dorsal and ventral divisions of the preiventricular system occur in the mesencephalic central gray matter. Thompson (114) considered only the ventral portion to be the dorsal longitudinal fasciculus.

Bucher and Burgi (18) considered the annulo-perifornical system to be only a subdivision of the dorsal longitudinal fasciculus. Marburg (69) called the periventricular system of fibers, including the dorsal longitudinal fasciculus, the fasciculus periependymalis, thus supporting Thompson's findings in fact, if not in terminology. While there is not complete agreement among the many authors as to the make up of the dorsal longitudinal fasciculus, they are in even less accord in their nomenclature.

In a more detailed account of the dorsal longitudinal fasciculus, Crosby and Woodburne (36) used the term dorsal longitudinal fasciculus in its widest sense, as a series of periventricular, ascending and descending, fascicles from the preoptic and hypothalamic levels to the caudal end of the brainstem. They observed that the rostral portion was made up of fascicles which inter-connect the hypothalamus and the dorsal thalamus. To differentiate this portion from the main mass of the system, they named this the thalamic portion, and divided it into four bundles: A, B, C and D. Bundle A connected the nucleus reuniens, the anterior periventricular nucleus, the anteroventral thalamic nucleus, and the preoptic area to the paraventricular nucleus of the hypothalamus. Bundle B passed from the dorsal thalamus to the dorsal hypothalamic area, the paraventricular nucleus and the anterior hypothalamic nucleus. Bundle C ran between the dorsal thalamus, the dorsal hypothalamic area and the dorsomedial hypothalamic nucleus. Bundle D

connected the ventromedial hypothalamic nucleus and the posterior hypothalamic area.

Crosby and Woodburne (36) described the brain stem portion or main mass of the dorsal longitudinal fasciculus as beginning rostrally near the edge of the third ventricle. They state that it was joined by a large bundle from the posterior hypothalamic area as it passed caudally to enter the mesencephalon. This midbrain portion was thought to originate in all parts of the hypothalamus except the supraoptic and ventromedial hypothalmic nuclei.

Crosby and Woodburne (36) observed that upon entering the midbrain, the dorsal longitudinal fasciculus contributed some fibers to the nucleus of Edinger-Westphal, and gave off a second bundle, the tectal component, that continued to run caudally within the central gray to the level of the superior colliculus where it turned dorsally, exited the gray, and terminated in the superior colliculus.

They felt that these fibers acted as a pathway for olfactovisceral impulses to reach the caudal areas. Beginning at the level of the superior colliculus, the dorsal longitudinal fasciculus separated into lateral and medial portions. The lateral portion ran within the dorsal or dorsolateral area of the central gray matter and a majority of its fibers ended in the lateral nucleus of the central gray. The remainder of the lateral portion continued caudally to the superior salivatory nucleus. The medial portion ran just medial to the nucleus of Darkschewitch in the ventrolateral area of the periaqueductal gray matter and contributed to the dorsal nucleus of the raphé, the laterodorsal nucleus of the tegmentum and the adjacent tegmental gray. They traced the caudalmost extent of the medial portion to the tegmental gray of the pons,

the abducens nucleus and motor facial nucleus before the fibers reached the medulla where they passed into the medial reticular gray area.

In addition to the descending tracts, there are also numerous ascending tracts. Morest (76) made lesions in the dorsal tegmental nucleus and traced degeneration rostrally in the dorsal longitudinal fasciculus. He observed connections between the dorsal tegemental nucleus and the pretectal nucleus, the dorsomedial nucleus of the thalamus, the posterior hypothalamic region and the dorsal hypothalamic area. Cowan et. al, (24) also in a degenerating axon study, observed ascending fibers from the periaqueductal region via the periventricular fiber system within their annulo-perifornical system.

In addition to the dorsal longitudinal fasciculus, Thompson (114) observed two additional tracts within the central gray which she named (1) the dorsal habenulotegmental tract and (2) the ventral habenulotegmental tract. Both took origin in the lateral and medial habenular nuclei, and passed beneath the posterior commissure in company with the habenulotectal fibers. From here, the dorsal tract turned caudally and joined the dorsal longitudinal fasciculus within the central gray matter. The ventral habenulotegmental tract ran alongside the much larger habenulopeduncular tract, or fasciculus retroflexus of Meynert, until reaching the rostro-lateral surface of the interpeduncular nucleus. Here it curved caudodorsally in a sixty degree arc, joined the fascicles of the pedunculotegmental tract and entered the ventral area of the central gray matter at the level of the oculomotor nucleus. Although some fibers terminated here, the majority ran into and joined the dorsal longitudinal fasciculus.

Although Bucher and Bürgi (16, 17) and Morest (76) noted a direct or dorsal habenulotegmental tract as described above, Cragg (25, 26) did not confirm this in the rabbit. He did observe an indirect connection between the habenula and the dorsal tegmental nucleus via the interpeduncular nucleus, and Nauta (82), using a degenerating axon method of tracking also observed an indirect pathway which ran from the habenular nuclei to the interpeduncular nucleus and on to the central gray matter. In addition to the fasciculus retroflexus of Meynert, which appeared to him to originate chiefly in the medial habenular nucleus, he noted a more diffuse concomitant lateral fiber system that originated in the lateral habenular nucleus. Although the majority of the fibers of this lateral system passed laterally through the centre median complex and then caudoventrally through the mesencephalic tegmentum, a small number of them passed in a caudoventral direction within the periaqueductal gray matter. Although this contingent within the central gray was not specifically named, it appears to correspond with the dorsal habenulotegmental tract.

On the other hand, Marburg (70) found no evidence of any connection between the habenular nuclei and the central gray matter in the human, nor did Akagi and Powell (2) employing an axon degeneration study in cats.

Another group of fibers within the central gray substance was reported by Castaldi (22) which he called the tangential group since they appeared to leave the region of the gray and pass out into the tegmentum. This finding was confirmed by Weisschedel (119) and again, later, by Nauta (82) using his own staining technique for degenerating axons. Both the latter authors found that these tangential fibers, or "radiatio grisea tegmenti" as Weisschedel named them, passed not only to the tegmentum