Ascending projections from spinal cord and brainstem to periaqueductal gray and thalamus

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Chapter 1

GENERAL INTRODUCTION

The work presented in this thesis has been performed at the Department of Anatomy and Embryology of the University Medical Center Groningen. For more than a decade, research in this department has focused on the neural pathways involved in the so-called emotional motor system as defined by Holstege (1997).

THE EMOTIONAL MOTOR SYSTEM

The emotional motor system, together with the somatic motor system, make up the brain’s ‘motor system’ (fig. 1), which is responsible for the neural control of all movements. The emotional motor system, in contrast to the somatic motor system, originates in the emotional, or limbic, parts of the brain. It controls basic behaviors important for the survival of either the individual or the species. The emotional motor system consist of a lateral and a medial part (fig. 1). The lateral part, which involves brain structures located in the lateral part of the brain, coordinates specific survival behaviors such as fight, flight or freezing behavior, micturition (release of urine), vocalization, mating.

**Motor system**

**Somatic motor system**

- Lateral
  - independent movements of the extremities
    - lateral cortico-spinal tract
    - rubro-spinal tract
  - eye-, neck, axial and proximal body movements
    - interstitio-spinal tract
    - vestibulo-spinal tract
    - tecto-spinal tract
    - reticulo-spinal tract
    - medial cortico-spinal tract

**Emotional motor system**

- Lateral
  - specific emotional behaviors
    - descending pathways from the PAG and other limbic structures

- Medial
  - gain setting systems including triggering mechanisms of rhythmical and other spinal reflexes
    - (sub-)coeruleo-spinal tract
    - ventral medullary reticulo-spinal and raphe-spinal tracts

**Basic system**

(premotor interneurons)

**Motoneurons**

Figure 1 Schematic overview of the subdivisions of the somatic and emotional motor system (Holstege, 1997).
behavior and maternal behavior. The medial part of the emotional motor system, which involves more medially located brain structures, regulates general level setting systems, such as nociception control (reduction of pain) and gain setting systems for the motoneurons.

No motor system, neither somatic nor emotional, can function without input from the environment. Many, if not all, of our actions are in fact re-actions. Changes in the environment direct our actions in every day live. If we feel cold, we put on a sweater, if we see a red light we hit the brakes, if we hear the phone ring we pick it up. Many of these reactions are conscious, but sometimes we also react to input from our environment unconsciously. We retract our hand before we realize the pan is hot, we duck before we realize something was flying our way, we turn our heads towards a loud sound before we realize where it came from. We become conscious of these re-actions only after they have happened. Other re-actions of our body remain unconscious most of the times. The muscles in our pupils contract when we are exposed to more light, digestive juices are released after we have consumed food, the blood in our skin is rerouted to our organs when we become colder. Et cetera, et
cetera. In order for the muscles to move body parts in an appropriate way, the brain needs input, about the internal and external environment, but also about what other parts of the brain are doing.

Because of the importance of the afferent limb (from Latin ad+ferre: to bring to) for the emotional motor system, research in the Department of Anatomy in Groningen has not only been focused on the output of this system, but also on its input. Dr. L.J. Mouton of this department, in her thesis (1999) stated that the ‘emotional motor system’ should actually be called the ‘emotional sensorimotor system’, because the afferent limb of a functional circuit is just as important as its efferent limb (from Latin ex+ferre: take away from). Moreover, specific sensory information is transmitted to specific brain structures involved in the emotional motor system. Research on the input to the emotional motor system has mainly been focused on the afferents of the midbrain periaqueductal gray (PAG; fig. 2), which is a key structure in the emotional motor system. It is sometimes considered the most caudal part of the limbic brain, and electrical or chemical stimulation in the PAG has been shown to be able to elicit all of the basic survival behaviors, such as fight, flight and freezing, micturition and mating posture.

Figure 3. Schematic representation of the location of the thalamus (in dark gray) with anterior-posterior coordinates according to Berman and Jones’s atlas (1982) of the cat.
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All work presented in this thesis was performed in the context of research on the ‘emotional sensorimotor system’. The first part of the thesis concerns input from the brainstem to the PAG. Projections from the spinal cord to the PAG had been studied thoroughly, but projections from the brainstem to the PAG had not yet been studied in such detail.

In order to be able to place the pathways of the ‘emotional sensory system’ in perspective with other ascending tracts, an attempt was made to compare them to the pathway from the spinal cord to the thalamus, the so-called spinothalamic tract. The thalamus (fig. 3), located in the diencephalon, is usually seen as the ‘gateway to the cortex’; all sensory input that reaches the cortical areas, after which awareness of the sensation can occur, travels to the thalamus first. The focus both in research and in teaching of the sensory system has always been on the pathways to the thalamus. Thus, the thalamus has become the best known receiver of sensory information from the spinal cord. A precise comparison of the spino-PAG pathway, that has been studied thoroughly in our laboratory (VanderHorst et al., 1996, Mouton et al., 1997; Mouton and Holstege, 2000, Mouton et al., 2001), and the spinothalamic tract was impossible, because no comprehensive studies on the spinothalamic tract in cats existed. To allow for careful comparison with the ‘emotional sensory’ pathways, afferents from the spinal cord to the thalamus were studied, using the same methods as in studies on the spino-PAG pathway. The second part of this thesis is comprised of these studies concerning the spinothalamic tract.

NEURAL PATHWAYS: ANATOMICAL TRACT TRACING STUDIES

All research done for this thesis was performed in cats, whose brains are relatively good models for the human brain. The aim of this and of most other neuroanatomical

Figure 4. Schematic representation of retrograde and anterograde transport of an injected neural tracer (in gray).
research, is to learn more about the human central nervous system, possibly contributing to solutions for disease. Although research techniques have been developed to study the living human brain, such as electro encephalograms (EEG), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), many questions still can only be answered through animal research.

In the studies presented here, neural tracing techniques were used, for both anterograde and retrograde tracing (fig. 4). With this technique, a neural tracer is injected in the brain area of interest, where it is taken up by the axons and/or neurons in that area. Retrograde tracing occurs when the tracer is taken up by an axon terminal and transported back to the cell body, resulting in labeled cells (fig. 4). Anterograde tracing occurs when the tracer is taken up by a cell body or its dendrites and transported anterogradely to the end of the axon, resulting in labeled fibers and terminals (fig. 4). After histochemical processing, labeled cells and terminals can be made visible by light-microscopical techniques.

Afferents from the Brainstem to the Periaqueductal Gray

No studies exist that provide an overview of all projections from the brainstem to the PAG in cats. Retrograde tracing studies in other species have shown that cells projecting to the PAG are mainly located in the tegmental field and in a large variety of brainstem nuclei, including the parabrachial nuclei, the nucleus of the solitary tract, dorsal column nuclei and the caudal spinal trigeminal nucleus (rat: Marchand and Hagino, 1983; Morrell and Pfaff, 1983; Beitz, 1982; rabbit: Meller and Dennis, 1986; monkey: Mantyh, 1982). Other studies focused on the projections of one particular brain stem area to the midbrain. These studies provided anterograde tracing data showing the termination pattern of brainstem fibers within the PAG. This termination pattern is important, because the PAG consists of different columns (fig. 5) each with different functions (Bandler et al., 1991; Bandler and Shipley, 1994). It was shown that from the spinal trigeminal nucleus and the dorsal column nuclei projections reach the lateral column of the PAG in cat and monkey (Wiberg and Blomqvist, 1984a; Wiberg et al., 1986; Wiberg et al., 1987), while cells in the nucleus of the solitary tract send

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Figure 5. Schematic representation of the different columns of the periaqueductal gray (Bandler et al., 1991; Bandler and Shipley, 1994).
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their axons to mainly the ventrolateral column of the PAG (Herbert and Saper, 1992). Projections from the tegmental field of pons and medulla reach the dorsomedial, lateral and ventrolateral columns of the PAG (Herbert and Saper, 1992; Vertes et al., 1986; Illing and Graybiel, 1986). Brain stem projections, like spinal projections, have been described to avoid the dorsolateral column of the PAG.

Scope of this thesis

In this thesis three pathways from brainstem to PAG that had not been reported before, are described. One of these pathways was from the nucleus retroambiguus (NRA) to the PAG. The NRA is a specific cell group located in the lateral tegmental field of the caudal medulla. It contains the premotor interneurons that in turn project to motoneurons of muscles involved in vocalization, vomiting, respiration and mating behavior (Merrill, 1974; Miller, 1987; Holstege, 1989; VanderHorst and Holstege, 1995). As target area of the lateral emotional motor system, it receives direct projections from the PAG. In chapter 2 projections in the opposite direction, from the NRA to the PAG, were described and the possible role in feedback of this pathway was discussed. In chapter 3 projections from the nucleus prepositus hypoglossi, located in the dorsal pons and medulla, to the dorsolateral column of the PAG were described. This pathway is remarkable, because projections from cells in pons and medulla, like those in the spinal cord, have always been assumed to avoid the dorsolateral column. Because the nucleus prepositus hypoglossi is involved in the oculomotor system, it was hypothesized that the dorsolateral PAG plays a role in this system. In search for projections from other oculomotor related brain stem areas to the dorsolateral PAG, the pathway originating in the periparabigeminal area in the midbrain was also studied (chapter 4).

AFFERENTS FROM THE SPINAL CORD TO THE THALAMUS

The spinothalamic tract is known for its role in the conduction of nociceptive and thermal information, but it also relays other somatosensory input, such as light touch.
pressure, and joint and muscle stimulation (Willis and Coggeshall, 2004 for review) to the thalamus. The thalamus is a large structure in the diencephalon and exists of many different functional nuclei (fig. 6). Anterograde tracing studies on the spinothalamic tract in cat have shown that projections from the spinal cord to the thalamus reach a
large number of these nuclei. From the enlargements, spinal fibers project mainly to the paraventricular nucleus of the thalamus, the centrolateral nucleus, the paracentral nucleus, the submedial nucleus, the caudal posterior complex, the ventral edge of the ventroposterior nuclei and the ventrolateral nucleus (Craig and Burton, 1985). The cells of origin of the spinothalamic tract are located in different areas of the spinal cord, called laminae (fig. 7; Rexed, 1954). Spinothalamic projections are usually associated with cells in lamina I, but retrograde tracing studies in rat, cat and monkey (rat: Kemplay and Webster, 1986; Burstein et al., 1990b; cat: Trevino et al., 1972; Trevino and Carstens, 1975; Carstens and Trevino, 1978a; Carstens and Trevino, 1978b; Comans and Snow, 1981; Wiberg and Blomqvist, 1984b; monkey: Trevino and Carstens, 1975; Willis et al., 1979; Apkarian and Hodge, 1989a) have shown that spinothalamic cells are also present in the deep dorsal horn (laminae V and VI), and laminae VII and VIII in all three species. Moreover, spinothalamic neurons can be found in laminae II and III in rat, and in laminae II, III and IV in monkey.

Comprehensive qualitative and quantitative studies of spinothalamic projections exist in rat (Kemplay and Webster, 1986; Burstein et al., 1990b) and monkey (Apkarian and Hodge, 1989a), but not in cat, although this species is widely used in studies of the spinothalamic tract.

Scope of this thesis

The spinal afferents of the thalamus were studied in all laminae and in all segments of the spinal cord in cat (fig. 7). To allow careful comparison with the spino-PAG tract the same techniques were used as in the study on spinal projections to the PAG (Mouton and Holstege, 2000). After large injections in the thalamus, the total number of spinothalamic neurons was estimated (chapter 5), as well as the percentage of these neurons that was located in lamina I (chapter 6). When the laminar and segmental distribution of all spinothalamic neurons was studied (chapter 7), it was found that at least five clusters of neurons project from the spinal cord to the thalamus. The location of these clusters showed remarkable similarities to the location of spino-PAG neurons, which had been described by Mouton and Holstege (2000). Although the similarities between the location of spinothalamic clusters and spino-PAG clusters were striking, further study also revealed differences.

Three studies were performed to specifically compare spinothalamic projections with spino-PAG projections. Comparisons were made between the number of lamina I neurons projecting to the thalamus, to the PAG and to the parabrachial nuclei (PBN), and it was found that more lamina I cells project to PBN and PAG than to the thalamus (chapter 8). In chapter 9 the number and precise location of the cells in the upper cervical spinal cord projecting to PAG or thalamus were described. Furthermore projections from the lateral sacral cord to the PAG, and the lack of these projections to the thalamus, were demonstrated (chapter 10).