CORTICOFUGAL PROJECTIONS TO THE MIDBRAIN PERIAQUEDUCTAL GRAY MATTER

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An important role in the mechanisms of pain and reflex analgesia is played by the periaqueductal gray matter (PAG) of the midbrain. Electrical stimulation or microinjections of opiates into this structure has been shown to produce a precise analgesic effect [9, 12]. Depression of pain sensitivity and marked activation of endorphinergic systems of PAG are observed during acupuncture and in response to stress [1, 3]. Electrolytic blocking of PAG leads to a marked decrease in the analgesic effect of morphine, acupuncture, and stress [2, 14].

There is electrophysiological evidence of the modulating effect of somatosensory cortical area II on conduction of nociceptive impulses to PAG [5]. However, morphological studies of direct cortical connections with PAG have been few in number and they have mainly dealt with projections of the prefrontal and limbic cortex with PAG [8, 10].

The object of this investigation was to study direct corticofugal projections to PAG as the morphological substrate of cortical influences on one of the antinociceptive structures of the brain.

EXPERIMENTAL METHOD

Experiments were carried out on 11 adult cats. Under pentobarbital anesthesia (40 mg/kg), using a stereotaxic technique and taking coordinates from Berman's atlas [7], a unilateral microinjection of 0.08–0.15 μl of a 50% aqueous solution of horseradish peroxidase (HRP, from Sigma) was given in the course of 30 min into the rostral and caudal zones of PAG in the midbrain. The animal's brain was perfused 48–72 h later with a mixture of 0.4% paraformaldehyde and 1.25% glutaraldehyde, made up in 0.1 M phosphate buffer, pH 7.4. Subsequent treatement of the brain was in accordance with Mesulam's method [13].

EXPERIMENTAL RESULTS

In experiments with unilateral injection of microdoses of HRP into different parts of PAG it was found that retrogradely labeled neurons were located ipsilaterally in various regions of the cerebral cortex. All labeled cells in the cortical regions were located in layer V, the neurons of which are the main source of cortical efferent fibers to the various subcortical brain formations.

Pyramidal neurons, filled with HRP granules, were found in somatosensory cortical area II (SII; Fig. 1a), situated in the anterior ectosylvian gyrus. Labeled cells in this region were found independently of the localization of the injected HRP in PAG, but their number was rather less compared with other cortical regions.

Labeled cells were observed in somatosensory cortical area I (Fig. 1b), situated in the posterior cruciate and coronal gyri. It was found that the distribution of labeled neurons in this region of the cortex depends on the site of injection of HRP into PAG. For instance, if HRP was injected into the lateral areas of the rostral zone of PAG, many labeled cells were seen in the coronal gyrus and only single neurons in the posterior cruciate gyrus (Fig. 2). After injection of HRP into the dorsal part of PAG, single labeled cells were found only in the coronal gyrus (Fig. 3).

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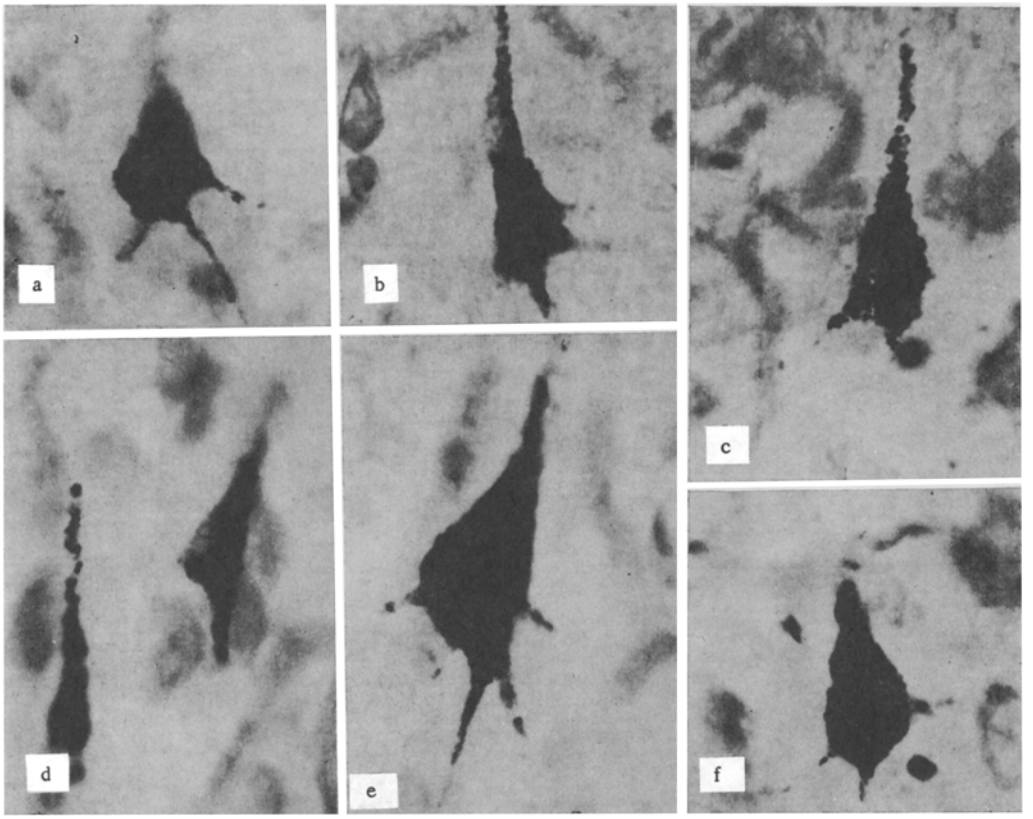

Fig. 1. HRP-labeled pyramidal neurons in layer V: a) in somatosensory area II; b) in somatosensory area I; c, d) in cingulate cortex; e) in insular cortex; f) in prefrontal cortex. MBI-15 microscope, ojective 40, ocular homal 1.6.

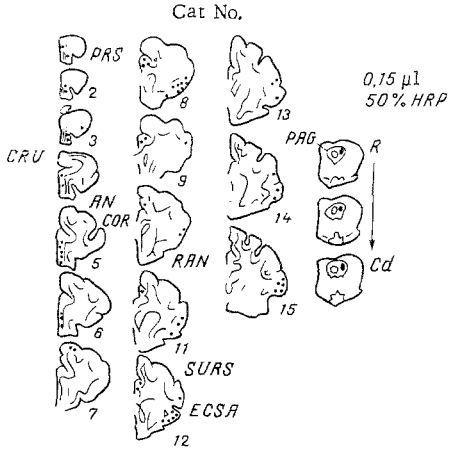

Fig. 2. Schematic distribution of labeled neurons (dots) in frontal sections of cat cortex after injection of HRP into lateral area of rostral zone of PAG. Here and in Fig. 3: AN) s. ansatus; Cd) candalis; Cor) g. coronalis; CRU) g. cruciatus; ECSA) g. ectosylvius ant; GEN) s. genualis; HRP) horseradish peroxidase; PAG) peri-aqueductal hray; PRS) s. presylvius; RAN) s. rhinicus; SCC) s. supracallosalis; SUPS) suprasylvius; SYL) g. sylvius.

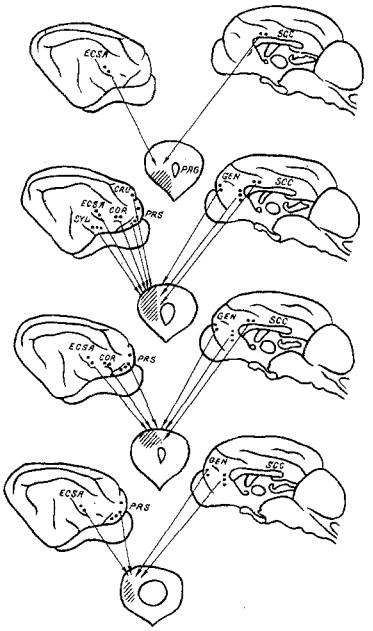

Fig. 3. General scheme of distribution of cortical projections into different areas (ventral, lateral, and dorsal) of rostral and caudal (lateral areas) zones of PAG.

In the prefrontal cortex, which includes the frontal zones of the lateral surface of the proreal gyrus, and frontal and rectal gyri on the medial surface, labeled neurons also were observed (Fig. 1f). The character of distribution of labeled neurons in the prefrontal region depends on the location of injection of HRP into PAG. Labeled neurons were found on both the lateral and the medial surfaces of the prefrontal cortex only if HRP was injected into lateral and dorsal areas of the rostral zones of PAG, and also into the lateral areas of the caudal zone of PAG (Figs. 2 and 3).

Labeled cells were found in the cingulate cortex, which is located in the cingulate and genual gyri (Fig. 1c, d). The character of distribution of labeled cells in these gyri depends on the site of injection of HRP into different areas of PAG (Fig. 3). If HRP was injected into the dorsal and lateral areas of the rostral zone of PAG, many labeled neurons were observed in the genual gyrus and only a few labeled neurons in the cingulate gyrus. If HRP was injected into the ventral areas of the rostral zone of PAG, single labeled cells were discovered only in the cingulate gyrus. If HRP was injected into the caudal zone of PAG (lateral areas) many labeled neurons were found only in the genual gyrus. Labeled cells also were found in the insular cortex (in the anterior sylvian gyrus). This region of the cortex is distinguished by the selectivity of its projections, neurons of which send their axons only into the lateral areas of the rostral zone of PAG (Fig. 1d, Figs. 2 and 3).

PAG thus receives direct projections from cortical areas SII and SI, and the prefrontal, cingulate, and insular cortex. However, the cortical projections differ in their location in PAG: Neurons of SII send diffuse projections to all parts of the rostral and caudal zone of PAG, neurons of SI send projections to dorsolateral areas of the rostral zone of PAG, neurons of the prefrontal cortex send projections to the dorsolateral areas of the rostral zone and to the lateral areas of the caudal zone of PAG, neurons of the cingulate gyrus send projections to all areas of the rostral zone, those of the genual gyrus to the dorsolateral areas of the rostral zone and to the lateral areas of the caudal zone of PAG, while neurons of the insular cortex send projections into the lateral areas of the rostral zone of PAG.

The fact that SII sends direct projections to all areas of the rostral and caudal (lateral area) zones of PAG is particularly interesting in connection with the view that SII is the central modulator of nociceptive sensation, whose function is connected with mechanisms of primary analysis and identification of extremal stimuli or situations, and also the activation of the necessary defensive mechanisms (including antinociceptive) for the formation of an adequate response of the organism to the noxious factor [5].

Projections of SII to all parts of PAG, discovered in this investigation, confirmed the view that this cortical region may have a direct influence on the activity of neuronal mechanisms of PAG [5].

Besides this, an important role in the regulation of antinociceptive mechanisms and, in particular, those responsible for controlling the emotional-affective component, is played by the prefrontal cortex and the limbic cortex, which includes the cingulate and insular zones of the cortex. Clinical and experimental data are evidence in support of this view. Frontal lobotomy, undertaken for the treatment of chronic pain, has been shown to cause considerable depression of emotional pain responses, although the threshold of nociceptive sensation remains unchanged or is actually lowered [15]. Morphine, in small doses, has a similar action on the emotional component of the pain response [4, 6]. The existence of direct descending connections of cortical zones responsible for the control of emotional reactions, under the influence of nociceptive stimuli, to PAG thus seems proved beyond dispute. In fact, in experiments on monkeys, neurons of the prefrontal, insular, and cingulate cortex were shown to send direct projections to dorsolateral areas of PAG [8]. In experiments on cats, we obtained evidence that the prefrontal, insular, and cingulate cortex send direct projections to the rostral (lateral and dorsal areas) and caudal (lateral area) zones of PAG.

Electrical stimulation of these regions of PAG, incidentally, causes depression of pain sensitivity, often accompanied by emotional or motor responses [11]. Comparison of these data with the results of our experiments leads to the conclusion that neurons in these regions of PAG, first, receive impulses from the cortical regions of the brain and, second, they may participate directly in the regulation of emotional behavior, probably on account of ascending projections from PAG.

The mechanisms of neuronal activity at the PAG level are thus under the direct influence of the limbic, prefrontal, and somatosensory areas II and I of the cerebral cortex.

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