THE EFFECT OF ANALGESICS ON VARIOUS COMPONENTS OF THE BULBAR RESPIRATORY CENTER

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When the action of analgesics on the central nervous system is described it is constantly stressed that these compounds depress the respiratory center. However, this statement is not precise enough, for it reflects neither the localization nor the direction of the action of analgesic drugs. Because of the complex morphological and functional organization of the respiratory center, we have undertaken a more detailed investigation of the effect of morphine and trimeperidine on the various components of the bulbar respiratory center.

EXPERIMENTAL METHOD

Part of the cerebellum was removed from decerebrate cats and access laid open to the floor of the fourth ventricle. Two or three unipolar electrodes, 50 μ in diameter and insulated throughout their length (except at the point), were introduced into various structures of the medulla. Stimulation was applied in the form of short series (15 sec) of rectangular impulses with a duration of 1 millisec, a frequency of 30-60 cps, and a voltage of 0.5-2 V. The localization of the stimulus in each experiment was determined in brain sections by the method developed in our laboratory [6]. The respiratory response reactions were recorded by a pneumograph through a cannula inserted into the interpleural space.

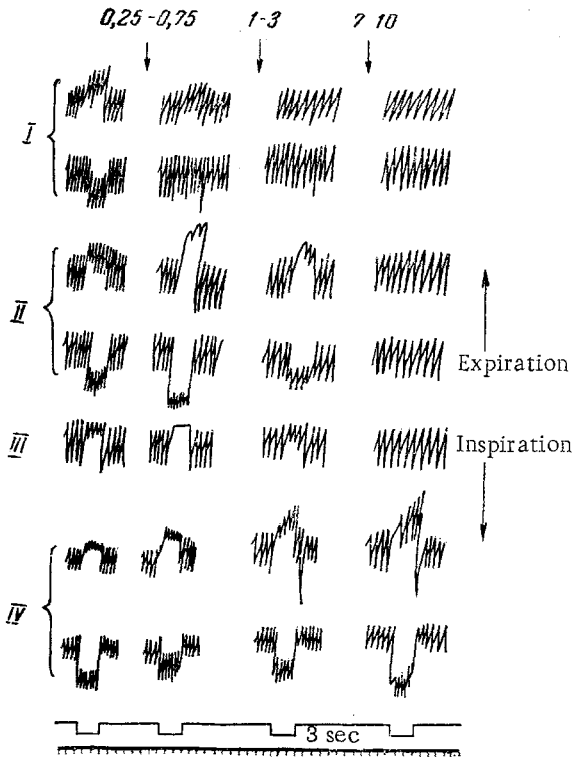

Fig. 1. Schematic representation of the different types (I, II, III, IV) of respiratory responses and their change under the influence of analgesics. The figures at the top denote the doses of morphine and trimeperidine (in mg/kg).

EXPERIMENTAL RESULTS

When local stimulation was applied to various points in the region of the floor of the fourth ventricle, both inspiratory and expiratory respiratory reactions developed. The former were found predominantly during the stimulation of the more caudal and ventral segments of the reticular formation of the medulla, the latter during stimulation of the rostral and dorsal segments.

The whole varied series of respiratory responses arising during stimulation of the various divisions of the respiratory center, and the change in these reactions following administration of the analgesics (the experimental results cover 44 points of stimulation,

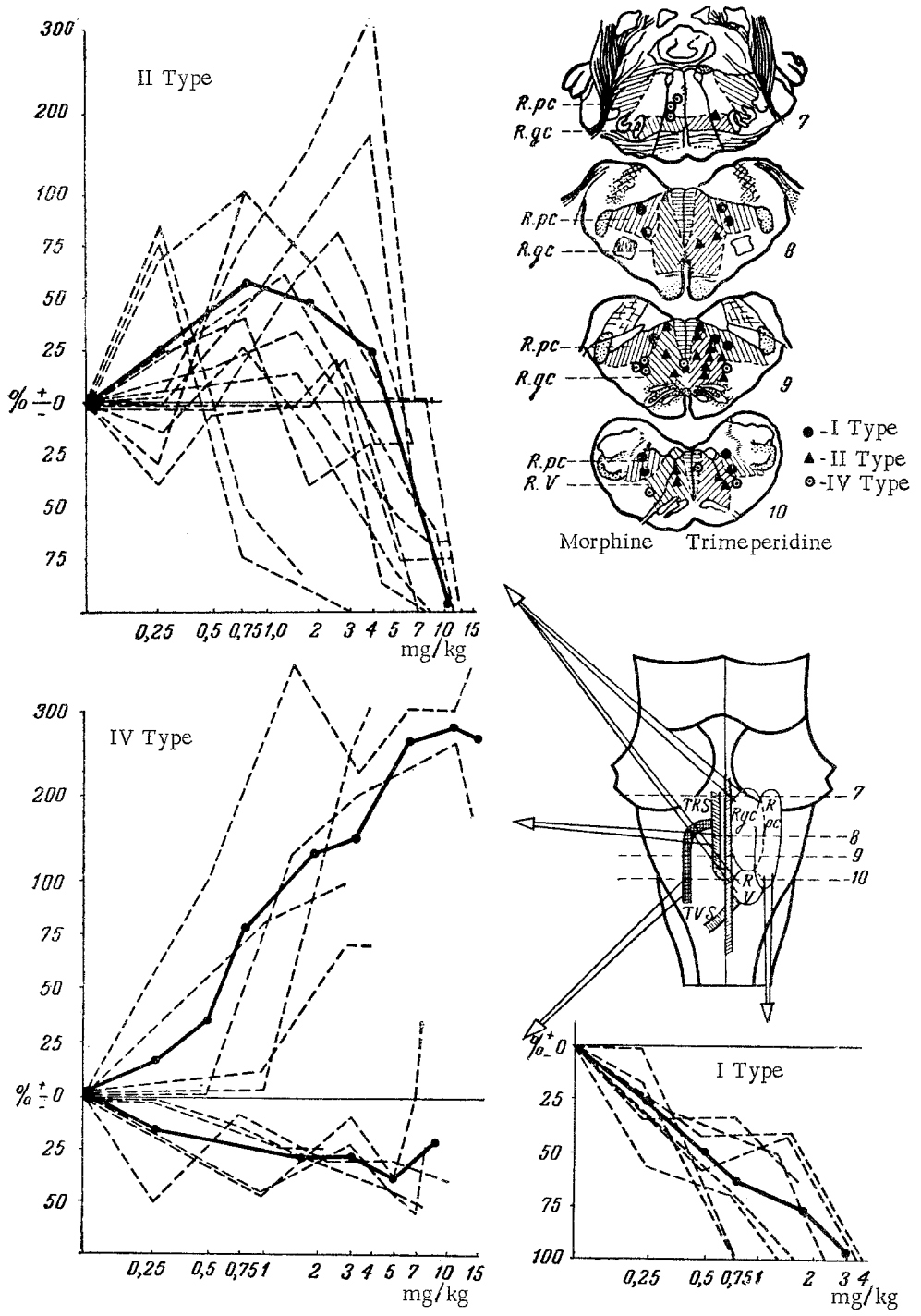

Fig. 2. Effect of increasing doses of morphine and trimeperidine on respiratory reactions caused by stimulation of various reticular nuclei. On the graphs, along the axis of ordinates —dynamics of changes in amplitude of respiratory reactions (in % of initial level) under influence of various doses of morphine and trimeperidine; along the axis of abscissas—doses of morphine and trimeperidine (logarithmic scale). Thick line—mean data. Brain sections 7-10 show the localization of the stimulation, the type of the respiratory response, and the changes resulting from the administration of analgesics. In the center, in schematic form —projection of the main morphological structures of the reticular formation on to the floor of the fourth ventricle. The lines 7-10 correspond to the sections of the cat's medulla (according to Brodal [13]) and the points of stimulation and conventional indices of the type of response reaction are shown. R. pc—parvocellular reticular nucleus; R. V —ventral reticular nucleus R.gc—giant-cell reticular nucleus; TRS—reticulospinal tract; TVS—vestibulospinal tract.

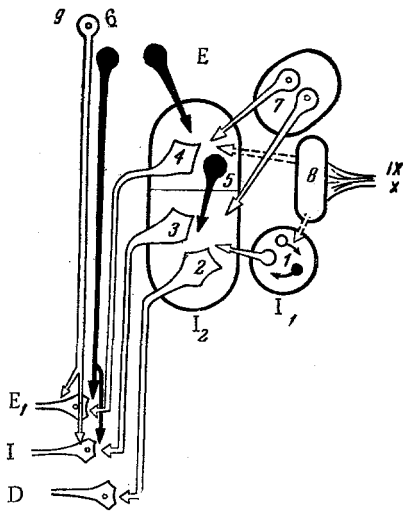

Fig. 3. Scheme of the functional organization of the bulbar respiratory center.

the location of which was confirmed), may be reduced to 4 principal types (Fig. 1). The action of the analgesics varied, depending on the type of the respiratory reaction and the localization of the stimulus, and the action took the form of either an increase or a decrease in the intensity of the response reactions.

An inspiratory shift of small amplitude, with an increase in the respiration rate, or an expiratory shift with a slowing of respiration (type I) developed in response to stimulation of the dorso-lateral reticular formation, mainly in the region of the parvocellular reticular nucleus (Fig. 2). With no preliminary facilitation, this reaction was depressed by small doses of analgesics (a decrease in the amplitude of the shift after administration of trimeperidine or morphine in a dose of 0.25-0.5 mg/kg, and it was completely suppressed after administration of 2-3 mg/kg).

The respiratory reactions arising during stimulation of the reticular nucleus of the tegmentum of the medulla (in Brodal's terminology, the magnocellular and ventral reticular nuclei [13]) showed an initial increase in amplitude (type II) under the influence of small doses of analgesics. With an increase in the dose of the analgesics the rhythm of the background respiration was slowed, but the amplitude of the shifts towards expiration or inspiration continued to increase (Figs. 1 and 2). A slowing of the respiration rate, often observed at the height of the expiratory shift, was abolished by the action of the analgesics. After the total suppression of the inspiratory or expiratory reaction under the influence of large doses of analgesics, no changes took place in the respiration rate during stimulation.

In response to stimulation of certain zones of the reticular formation (dorsal and rostral regions of the giant-cell nucleus, the paragigantocellular nucleus in Taber's terminology [20], a respiratory reaction of a unique type developed. With no shift in phase, a decrease in the amplitude of the respiratory excursions took place, with a marked restriction of inspiration (type III). This direction was expiratory in direction, but in essence it amounted to inhibition of inspiration. Under the influence of a small dose of analgesics (0.25 mg/kg) this reaction became stronger, so that complete inhibition of inspiration and arrest in the phase of expiration ensued. After a very slight increase in the dose of morphine or trimeperidine (up to 0.5-1.0 mg/kg) the expiratory pause disappeared.

Different changes took place in the respiratory reactions evoked by stimulation of the region traversed by the descending tracts (type IV). Morphine and trimeperidine, in doses of 1-3 mg/kg, caused a considerable (two- to threefold) increase in the amplitude of the inspiratory or expiratory shifts arising mainly in response to stimulation of the zone traversed by the medical reticulospinal tract. A further increase in the dose of morphine to 15 mg/kg was not followed by depression of the respiratory responses. The motor reactions evoked by stimulation of the region traversed by the vestibulospinal tract were not significantly changed by the action of the analgesics. The amplitude of the responses fell very slightly, but the reaction was not suppressed even after the administration of large doses (15 mg/kg).

The graphs given in Fig. 2 show the dynamics of the different types (I, II, IV) of changes in the respiratory reactions following administration of increasing doses of analgesics. In the case of the type III reactions the results could not be represented graphically, for no phase shift in respiration took place.

The effect of analgesics on the respiratory reactions arising during stimulation of the central segment of the divided left vagus nerve with rectangular stimuli of different frequencies was also studied in decerebrate cats. In accordance with data in the literature [2, 5, 7], in response to low-frequency stimuli (10-30 cps) inspiratory reactions predominated, and under the influence of small doses of morphine and trimeperidine (0.5-1.5 mg/kg) these were depressed or converted into expiratory reactions. In response to stimulation of higher frequencies (50-100 cps) expiratory reactions developed. These were not depressed, but in some cases they were facilitated, even when large doses of analgesics were used.

It follows from the results described above that the action of analgesics on the respiratory reactions obtained from the various morphological structures of the medulla is not the same. The essence of these facts may be

satisfactorily explained on the basis of the scheme of the functional organization of the bulbar respiratory center (Fig. 3) which we constructed from the results of our own experiments [4], in full agreement with data in the literature.

The change in the rhythm of the background respiration, which in our experiments began to appear after administration of trimeperidine in a dose of 0.5 mg/kg or morphine in a dose of 1 mg/kg, arises as a result of a lowering of the excitability of the primary inspiratory neurons (Fig. 3, 1). This complex network of neurons (Fig. 3, I_1) is not strictly localized in any particular morphological structures, but is represented in the lateral reticular nucleus [10, 14, 15, 18] immediately next to the nuclei of the tractus solitarius and the nucleus bigeminus [10, 11]. The primary respiratory neurons have no direct connections with the respiratory motoneurons of the spinal cord and they spread their excitatory influence to the secondary (effector) inspiratory (Fig. 3, 2 and 3) and expiratory (4) neurons, situated in the ventro-caudal segments of the medial reticular formation [8, 17], from which axons leave to the cervical and thoracic segments of the spinal cord [13]. These neurons (Fig. 3, 3) do not take part in ordinary respiration, but they facilitate the development of maximal inspiratory reactions, activating the motoneurons of the intercostal muscles (I). During selective stimulation of these neurons we observed the development of a considerable inspiratory shift, against the background of which the original respiration continued with its former rhythm and amplitude.

Under the influence of small doses of analgesics (0.25-1.0 mg/kg) an increase takes place in the amplitude of the respiratory responses during stimulation both of the medial reticular nuclei (inspiratory and expiratory zones) and of the region traversed by the reticulo- and tectospinal tracts. There are no grounds for assuming a primary stimulant action of analgesics on the reticular neurons. On the basis of a whole series of experiments conducted in our laboratory [1, 3] it has been shown that analgesics are capable of depressing various manifestations of inhibition in the central nervous system, including the inhibitory descending influences arising during stimulation of the reticular formation.

Hence, in this case also, the increase in the strength of the inspiratory reactions observed during stimulation of the region of the reticular nucleus of the tegmentum was brought about by the de-inhibitory action of the analgesics. Several authors [9, 19] have postulated the existence of inhibitory neurons [Fig. 3, 5 and 6) in the system of the respiratory center and this is confirmed by our experimental findings [4].

The inhibitory influences of the more rostral divisions of the brain stem are depressed more strongly by analgesics when smaller doses are used [3]. This explains the fact that the reactions of type III (expiratory depression of respiration without phase shift, i. e., inhibition of inspiration) arising during stimulation of the neurons (see Fig. 3, 5) of the expiratory zones were at first increased in strength after administration of morphine or trimeperidine in a dose of 0.25 mg/kg, so that complete inhibition of inspiration took place, but after a slightly larger dose of the same drugs these reactions completely disappeared (depression of neurons, 5). The rhythm of the background respiration underwent no further change. Only after administration of much larger doses of morphine and trimeperidine (7-10 mg/kg) did depression of the reticular neurons take place (3, 4), so that their stimulation no longer caused shifts in respiration.

The respiratory reactions arising in response to stimulation of the lateral reticular formations (Fig. 3, 7) were depressed by analgesics without preliminary facilitation. This took place because the zones from which these respiratory reactions developed are not true zones of the respiratory center. They are functionally connected by synaptic links to the inspiratory or expiratory zones. The analgesics very easily depressed these coupled reactions, presumably as a result of depression of the spread of excitation to the effector structures.

The respiratory reactions whose appearance was associated principally with excitation of the reticulospinal and vestibulospinal (Fig. 3, 9) descending tracts were not depressed even by large doses of analgesics, since these reactions are caused by direct activation of the spinal respiratory neurons (I, E_1).

The changes in respiration arising during activation of the system of the tractus solitarius (Fig. 3, 8), whether in response to direct stimulation or to reflex excitation (stimulation of the vagus nerve), were not depressed by the analgesics. Only a comparatively slight withdrawal of the inspiratory excitation (a spread of the flow of impulses to the primary respiratory neurons I_1) and its conversion into expiratory inhibition (the spread of excitation to the expiratory neurons E) or facilitation of the expiratory reactions (de-inhibition) was observed.

The view that the change in the respiratory reactions caused by the analgesics is largely due to the abolition of inhibitory influences on the respiratory neurons is confirmed by data in the literature [12]. In the only varying paper,

describing an investigation of the action of analgesics on the effect of stimulation of the respiratory center [16], the observations were made only on a small number of animals, using thick electrodes, and without determination of the localization of the stimulus. For these reasons, the assertions of these authors that analgesics only depress respiratory reactions evoked by stimulation of the inspiratory center cannot be regarded as convincing.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
