THE EFFECT OF PARTIAL EXTIRPATION OF THE PANCREAS ON THE DEVELOPMENT OF RECIPROCAL INHIBITION IN WARM-BLOODED ANIMALS

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The studies of A. V. Kibyakov and A. A. Uzbekov [4] on cold-blooded animals and those of O. D. Kurmaev [6] on warm-blooded animals have shown that the synthesis of acetylcholine depends directly on the function of the pancreas. The removal of the greater part of the pancreas weakened the inhibitory effect of the vagus nerve on heart activity and caused a parallel decrease in the amount of mediator – acetylcholine – escaping into the perfusion fluid. The disturbance of the acetylcholine formation process occurring with partial extirpation of the pancreas was due to a disturbance of the phospholipid metabolism, since the works of many authors [8, 7] have proven that the pancreas plays an important role in the regulation of the fat-lipoid metabolism of the body. These data make it possible to employ partial depancreatization as a method of intervention in the acetylcholine formation process. This operation essentially has no effect on carbohydrate metabolism since, according to the data of Minkowski [9] and others, $^9/_{10}$ of the pancreas in warm-blooded animals can be removed without any great change in the blood sugar level. The fact that the disturbance of acetylcholine synthesis caused by partial depancreatization is only temporary seems to be due to the compensatory functional intensification of the remaining glandular tissue. All disturbances of parasympathetic system activity in depancreatized animals were almost completely eliminated when the animals were given a compensatory injection of pharmacological acetylcholine.

In our preceding investigations [1], we proved that partial extirpation of the pancreas causes sharp disturbances in the activity of the spinal centers in frogs. At specific post-operative intervals (from the 7th to the 10th day), we often completely failed to obtain reciprocal inhibition of the semitendinosus muscle reflex contraction, which was clearly defined in animals which had not had the operation. In connection with this, we decided to conduct analogous studies on warm-blooded animals, including additional research on the changes in the lability of the nerve centers with the normal development of reciprocal inhibition and after partial depancreatization, since we had already obtained data [2] demonstrating the importance of acetylcholine to changes in the lability of the spinal centers.

EXPERIMENTAL METHODS

The experiments were conducted on dogs under ether-chloroform anesthesia. The reflex tetanic contraction of the semitendinosus muscle in response to short (19-20 seconds), repeated (every 40-50 seconds) stimulation of the peroneal nerve was recorded by the current of an induction coil fed by an accumulator of 3 volts. In other experiments, we used a stimulator to stimulate this nerve, which permitted us to vary the stimulation frequency from 3 to 500 impulses per second without stopping stimulation. The limits of the afferent stimulation optimum and pessimum frequency were used as a cross index of the corresponding spinal centers' lability level. Reciprocal inhibition of the flexor reflex being recorded was obtained by contralateral stimulation of the same nerve for a period of 4-7 minutes. Part of the experiments were conducted on dogs in which the greater part of the pancreas had been previously removed under sterile conditions. The experiments were done at different

post-operative intervals, beginning with the 2nd and ending with the 20th-22nd post-operative day. As a control, we injected some of the depancreatized animals intravenously with a compensatory injection of 1-3 ml of pharmacological acetylcholine, in a dilution of 1 : 100,000. The injections were done daily, or 1-2 hours before the experiment. A total of 83 experiments were conducted.

EXPERIMENTAL RESULTS

In the animals which had not had the operation (11 experiments), stimulation of the peroneal nerve (distance between inductorium coils – 100-120 mm) caused a well-expressed reflex contraction of the semitendinosus muscle. With the addition of contralateral stimulation (distance between inductorium coils – 80-100 mm), the reflex being recorded was sometimes first intensified and then inhibited, but in the majority of experiments this additional stimulation caused the immediate lessening of the reflex, changing subsequently into profound inhibition (Fig. 1, a). We did not observe in any of the experiments with the animals which had not been operated upon the inversion of reflex inhibition in the form of the reestablishment of the originally inhibited reflex, in spite of continuing "inhibitory" stimulation.

Removing the greater part of the pancreas from the experimental dogs (30 experiments) caused essential changes in the character of spinal activity. The most obvious change was a comparatively rapid "exhaustibility" of the reflex reactions. Even ipsilateral stimulation caused the pessimal inhibition of the semitendinosus muscle reflex contractions. The reflex "exhaustibility" was greatest on the 6th-10th days after the operation. In these cases, we had to terminate the experiment without testing the effect of contralateral stimulation. In these same experiments, when the semitendinosus muscle reflex contractions in response to the short, repeated tetanizations of the peroneal nerve were still sufficiently well expressed, we added continuous stimulation of the same, but contralateral nerve to the stimulation of the ipsilateral nerve. We observed no evident disturbances in the normal development of reciprocal inhibition during the first days after the operation (3rd-4th). At later post-operative intervals (beginning with the 5th-6th and ending with the 11th-12th days), it was very difficult to obtain the development of reciprocal inhibition of the flexor reflex being recorded in the experimental dogs. Although we could still observe a weak reciprocal inhibition of the semitendinosus muscle reflex contractions on the 5th-6th day, on the 7th-8th-9th day the flexor reflex was usually not inhibited under the influence of contralateral nerve stimulation, in spite of the fact that the conditions of nerve stimulation remained the same (Fig. 1, b). In several experiments, we observed the inversion of the reciprocal inhibition, in which, in spite of the continuing "inhibitory" stimulation, the initially inhibited flexor reflex was unexpectedly reestablished (Fig. 1, c); this was never observed in the animals which had not had the operation. By the 11th-12th day, the disturbances in the activity of the spinal centers had begun to subside. On the 14th-15th day, the development of extremely profound reciprocal inhibition was observed in almost all of the experiments conducted. The inversion, and occasionally the impossibility of obtaining reciprocal inhibition in the depancreatized animals was also observed on a background indirectly recording the lability, for which the limits of optimal stimulation frequency in ipsilateral nerve stimulation served as the index.

The experiments made with animals which had not had the operation (12 experiments) showed that the addition of contralateral nerve stimulation caused various changes in the character of the semitendinosus muscle reflex contraction. On a background of "inhibitory" stimulation, the limits of the afferent stimulation optimum frequency in the flexor reflex showed a tendency towards slower rates in the majority of experiments, thus indicating a reduced lability in the corresponding center; transitional parabiotic stages became apparent – the equalizing and the paradoxical (Fig. 2, a). Sometimes, the decrease in lability which occurred with the development of reciprocal inhibition was preceded by some tendency of the optimal stimulation limits toward faster frequencies. After the inhibitory stimulation was stopped, the reflex being recorded was rather quickly reestablished, and the optimal stimulation frequencies returned to the original high levels.

In experiments with depancreatized animals (16 experiments), an average decrease in the optimal stimulation frequency to 17-12 impulses per second could be observed, and a decrease to 6 and 3 impulses per second in separate experiments, whereas the optimal stimulation frequency in the animals which had not had the operation consisted of an average of 33-50 and even 80 impulses per second. In the depancreatized animals, a tendency to more rapid pessimal inhibition of the reflex was observed under the influence of ipsilateral stimulation. However, along with the tendency to direct pessimal inhibition, sharp disturbances occurred in the development of the connected reciprocal inhibition. In the depancreatized animals, contralateral nerve stimulation usually did

not cause a change in the optimal frequency limits of ipsilateral stimulation towards slower rhythms as was observed in the normal animals, but, on the contrary, in a series of experiments caused the optimal stimulation limits to shift toward faster rates with no subsequent decrease (Fig. 2, b). An inverted reaction often appeared: the lability reduction in the flexor reflex center which began under the influence of contralateral stimulation was suddenly replaced by an increase in the lability – the limits of optimal stimulation frequency shifted to higher levels (Fig. 2, c). In several experiments, a decrease in lability was subsequently observed; however, this lability reduction was maintained or even further reduced when the "inhibitory" stimulation was excluded. This indicates that the inhibition of the flexor reflex is not caused by the development of reciprocal inhibition, but by the direct inhibitory effect of the ipsilateral stimulation itself. Such disturbances were greatest on the 6th-12th post-operative days.

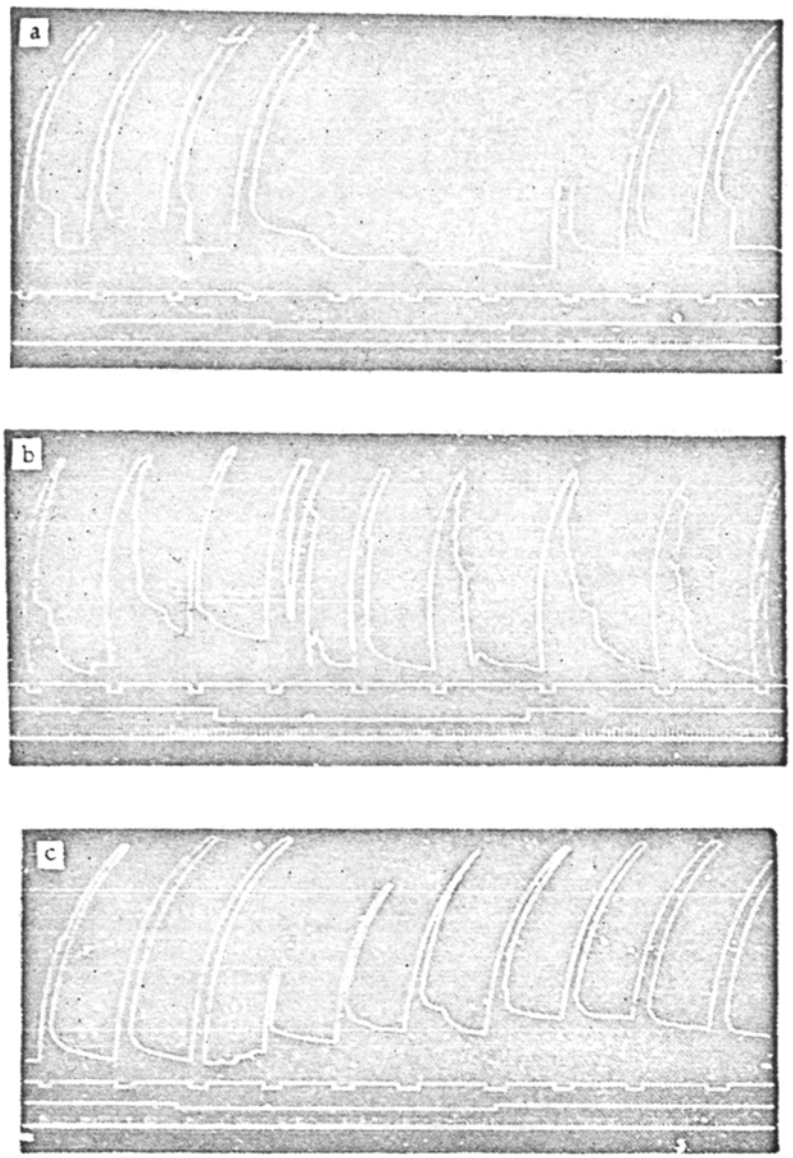

Fig. 1. The effect of partial depancreatization on the development of reciprocal inhibition in dogs.
a) development of reciprocal inhibition in dog which had not had the operation; b) absence of reciprocal inhibition on the 9th day after the operation removing part of the pancreas; c) inverted reaction on the 8th day after the operation. Curves from top to bottom signify: recording of semitendinosus muscle contraction; indication of peroneal nerve stimulation frequency; indication of contralateral stimulation; indication of time (in 5 second marks).

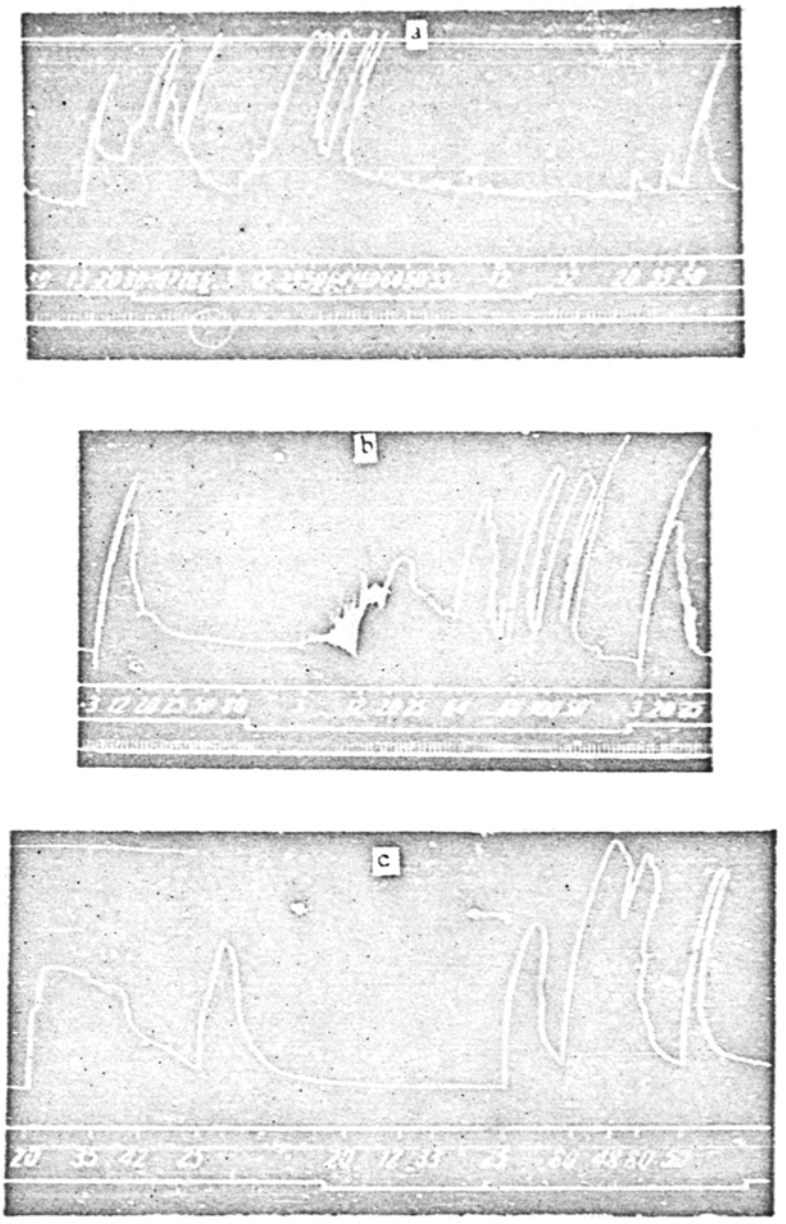

Fig. 2. Change of afferent stimulation optimal frequency on a background of contralateral nerve stimulation.
a) In dog which had not had the operation; b) on the 6th day after the operation partially removing the pancreas; c) on the 10th day after the operation. Curves mean the same as in Fig. 1.

In order to prove that the changes observed in spinal activity were specific, i. e. that they were due to the disturbance of the acetylcholine formation process, a group of the depancreatized dogs were injected with pharmacological acetylcholine (14 experiments). In the majority of cases in the control experiments, we succeeded in obtaining the development of reciprocal inhibition of the recorded reflex under the influence of contralateral stimulation (Fig. 3). This proved the specific character of the changes observed in the development of reciprocal inhibition in the depancreatized animals.

The changes we have described in the character of the reflex reactions of the animals operated upon are explained, we believe, by a change in the functional condition of the spinal centers, since the studies of L. N. Zeflrov and A. V. Kibyakov [3] and of A. V. Kibyakov and N. E. Piontak [5] have shown that acetylcholine

synthesis disturbance has no noticeable effect on the development of the tetanic form of skeletal muscle contractive activity in the peripheral neuro-muscular apparatus.

Fig. 3. Development of reciprocal inhibition after compensatory introduction of acetylcholine (9th day after operation). Curves mean the same as Figs. 1 and 2.

Analysis of the results obtained permits the conclusion that acetylcholine synthesis disturbance in dogs causes essential disturbances in the development of reciprocal inhibition: in spite of continuing "inhibitory" stimulation, reciprocal inhibition either completely fails to develop or shows an altered reaction in the form of the reestablishment of the reflex. In a series of cases, the direct inhibitory influence of ipsilateral stimulation was added. The inverted development of reciprocal inhibition has been described by N. E. Vvedensky as occurring with extremely strong or prolonged stimulation of a sensory nerve. N. E. Vvedensky believes this phenomenon to be due to the development of inhibition in the center of the "antagonistic" reflex arc, which caused the reflex reaction being recorded opposite to be disinhibited. We also observed a similar inversion of the reaction in the animals which had had the operation in response to stimulation of moderate force and duration of the "inhibitory" nerve: this can only be associated with the reduced lability of the nerve centers and their tendency to more rapid transition to pessimal inhibition caused by the disturbed synthesis of a nervous activity mediator such as acetylcholine. These data, which prove the important role of acetylcholine in regulating the functional condition of the spinal centers, can be used to help explain a series of symptoms attending diseases of the pancreas.

SUMMARY

The disturbance of the synthesis of acetylcholine in the organism of warm-blooded animals by partial removal of the pancreas with simultaneous ligation of its ducts causes disturbance of the spinal activity. The total level of lability of the nerve centers is decreased, transmission to the pessimal inhibition is more rapid, but simultaneously the development of reciprocal inhibition is altered. It either does not occur at all with the usual conditions of stimulation or shows altered reaction in the form of reestablishment of the reflex, notwithstanding the continuing "inhibitory" stimulation.

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