ELECTROPHYSIOLOGICAL ANALYSIS OF INTERACTION BETWEEN SEROTONIN AND γ-AMINOBUTYRIC ACID AT THE SEGMENTAL LEVEL OF THE SPINAL CORD

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Serotonin, an intermediate product of tryptophan metabolism, and γ-aminobutyric acid (GABA), formed in the body during glutamic acid metabolism, are normal products of brain metabolism and are present in considerable quantities in the central nervous system of vertebrates and man [3, 4, 14, 15].

The physiological action of these substances on the central nervous system has many features in common, and consists of inhibition of motor activity and of certain reflex responses [1, 2, 5-8, 10-13]. Meanwhile, the action of GABA on isolated organs has been found to be antagonistic to that of serotonin [9].

For this reason, a deeper analysis of the functional relationships between serotonin and GABA in the intact organism is of considerable interest, and the present investigation was carried out for this purpose.

EXPERIMENTAL METHOD

Experiments were carried out on 23 unanesthetized cats with the spinal cord divided at the level C7-T1. Observations were made on the changes produced by intravenous injection of serotonin* (25-55 μg/kg) and GABA† (0.5-1 mg/kg) and by their combined action in the amplitude of the potentials of an extensor monosynaptic reflex. The monosynaptic potentials were recorded by the method described previously [1].

EXPERIMENTAL RESULTS

Serotonin produced a sharp decrease in the amplitude of the potential of the monosynaptic reflex (on the average by 54%), which continued for 0.5-2 min and was then followed by an increase in its amplitude (on the average by 30%).

The course of these changes is illustrated in Fig. 1, reflecting the mean results of 10 experiments.

GABA produced similar, but less marked, biphasic changes in the monosynaptic potential. The mean decrease in amplitude of the potential in phase I of GABA action was 22% and it continued for 30 sec-1 min. The amplitude of the potential of the monosynaptic reflex then gradually increased and exceeded its initial level. The maximal increase of the potential averaged 18% of the initial amplitude of the reflex. Following repeated injections of equal doses of GABA in the course of one experiment its effect diminished, and in some cases it disappeared completely.

The results of an experiment in which GABA was injected intravenously in a dose of 0.54 mg/kg are given in Fig. 2. They show that the maximal decrease in amplitude of the potential, amounting in this experiment to 31%, was observed 30 sec after injection of GABA and was of very short duration. By 1.5 min after injection of GABA the amplitude of the reflex reached its maximum (114%), returning to its initial level after 3 min.

Because of the short duration of the GABA effect, maximal changes of potentials in phases I and II of action of GABA were observed in individual experiments at different time intervals after injection of the

*Serotonin creatinine sulfate from the firm Gee Lawson Chemicals Ltd., London, W. I.

† γ-aminobutyric acid (CF Panalysis) from the California Corporation for Biochemical Research, Los Angeles, 63.

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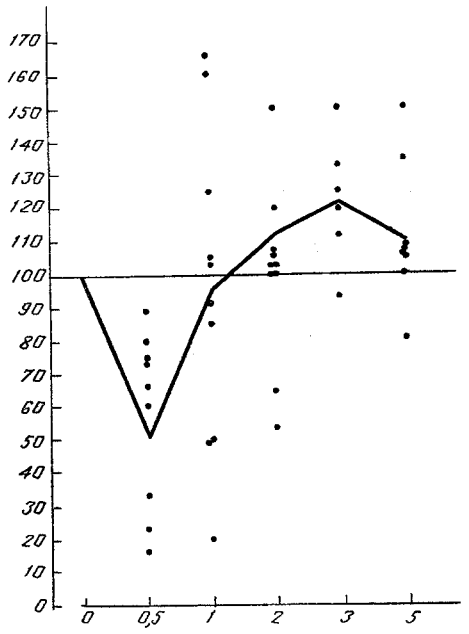

Fig. 1. Changes in amplitude of potential of monosynaptic reflex following intravenous injection of serotonin (25-55 μg/kg). Abscissa) time (in min), ordinate) changes in amplitude of potentials of monosynaptic reflex expressed in percent of initial magnitude (mean results of 10 experiments).

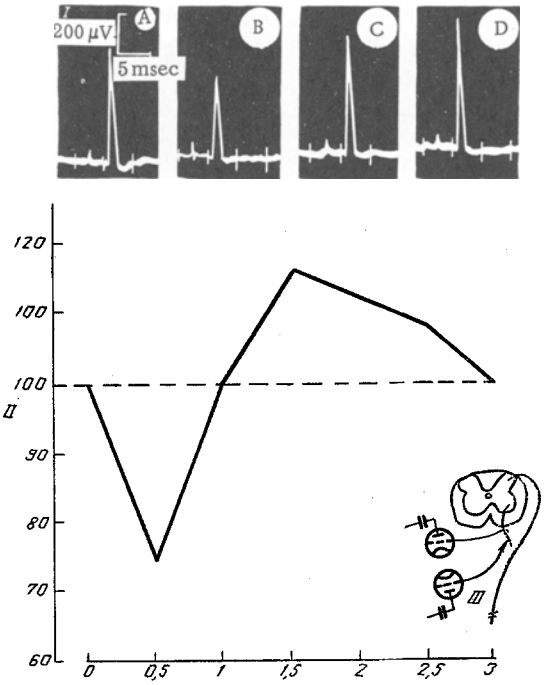

Fig. 2. Changes in amplitude of potentials of monosynaptic reflex following intravenous injection of GABA. I: A) Initial monosynaptic potential; B-D) monosynaptic potential 30, 40, and 90 sec respectively after injection of 0.54 mg/kg GABA into the ulnar vein; II) graph showing course of changes in amplitude of monosynaptic potential in time (values of coordinates the same as in Fig. 1); III) diagram showing position of recording and stimulating electrodes.

drug, complicating the graphic representation of the summated data reflecting dynamics of the changes in amplitude of the potentials in all the experiments. For this reason, the effects of serotonin and GABA are compared in future from the averaged numerical data.

Experiments in which GABA was given immediately after serotonin revealed the potentiating action of serotonin on the GABA effect in phase I of its action, expressed by a considerable (up to 81%) reduction of amplitude of the potentials of the monosynaptic reflex.

In the experiments of series II, in which injection of GABA preceded injection of serotonin, no appreciable change in the effects of the serotonin were observed.

The results of all the experiments are given in the table, generalizing the averaged (from 10 experiments) values of the maximal decrease and increase in amplitude of the potentials of the monosynaptic reflex expressed as percentages of their initial value.

The table shows that the greatest decrease in amplitude of the potentials of the monosynaptic reflex was observed as a result of successive injection of serotonin and GABA, when it reached 81%. This combined action of the two substances considerably exceeds the effect of each of them separately, and suggests the potentiating action of serotonin in relation to phase I of GABA action. The combined action of the two substances when given in the reverse order (GABA + serotonin) does not exceed the effect of serotonin itself.

The experimental results thus show that in the intact organism serotonin and GABA are not antagonists. On the contrary, these two substances have a unidirectional action on the amplitude of the monosynaptic potential, causing a considerable decrease in its value in phase I of their action.

Effect of GABA and Serotonin on Amplitude of Monosynaptic Reflex (Results in Percent of Initial Level)

substance injected	phase I–decrease in amplitude		phase II–increase of amplitude	
	$M \pm m$	P	$M \pm m$	P
GABA	22±2,6	<0,001	18±3,4	<0,001
serotonin	54±8,8	<0,001	30±7,8	<0,01
serotonin + GABA	81±5,5	<0,001	21±8	<0,05
GABA + serotonin	55±5,7	<0,001	28±7,6	<0,01

The decrease in amplitude of the potentials of the monosynaptic reflex observed under the influence of serotonin and GABA demonstrate a decrease in the excitability of the motoneurons under the action of these substances. The fact that the decrease in amplitude of the potentials of the monosynaptic reflex was more marked during combined action of serotonin and GABA injected in that order indicates their functional synergism. It is not yet clear why this synergism is not exhibited when these substances are given in the opposite order (GABA + serotonin). It may be assumed that the reason for this is the very short duration of phase I of GABA action. In the experiments in which GABA was injected before serotonin, the latter evidently reached the motoneurons in the phase of recovery of their excitation after its brief depression by the action of GABA. For this reason, the maximal decrease in amplitude of the potentials of the monosynaptic reflex under the influence of injection, first of GABA and then of serotonin, was almost equivalent to the effect of serotonin alone.

LITERATURE CITED

1. E. A. Gromova, S. A. Skuratova, and G. A. Romanova, Farmakol. i Toksikol., No. 4, 387 (1966).
2. A. D. Nozdrachev, In the book: Investigations into the Evolution of Nervous Activity [in Russian], Leningrad (1959), p. 217.
3. A. H. Amin, T. B. Crawford, and J. H. Gaddum, J. Physiol. (London), Vol. 126 (1954), p. 596.
4. J. Awapara, A. J. Landua, and R. Fuerst, J. Biol. Chem., Vol. 187 (1950), p. 35.
5. K. P. Bhargava and R. K. Srivastava, Brit. J. Pharmacol., Vol. 23 (1964), p. 391.
6. B. Brown, Ann. N. Y. Acad. Sci., Vol. 66, Art. 3 (1957), p. 677.
7. D. R. Curtis and R. Davis, Nature, Vol. 192 (1961), p. 1083.
8. W. Feldberg and S. Sherwood, J. Physiol. (London), Vol. 123 (1954), p. 148.
9. F. Hobbiger, Ibid., Vol. 144 (1958), p. 349.
10. M. Kuno, Proc. Jap. Acad., Vol. 36 (1960), p. 513.
11. Idem, Jap. J. Physiol., Vol. 11 (1961), p. 304.
12. A. S. Marazzi and E. R. Hart, Electroenceph. Clin. Neurophysiol., Vol. 7 (1955), p. 146.
13. A. Muneoka, Jap. J. Physiol., Vol. 11 (1961), p. 555.
14. E. Roberts and S. Frankel, J. Biol. Chem., Vol. 187 (1950), p. 55.
15. S. Udenfriend, H. Weissbach, and C. T. Clark, Ibid., Vol. 215 (1955), p. 337.