SOME EFFECTS OF BRADYKININ ON THE CENTRAL NERVOUS SYSTEM

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ALMOST no attention has been paid to the actions of bradykinin on the central nervous system in intact animals. Considering the importance of substance P, a polypeptide isolated from tissue in the central nervous system, it seems to us that a comparison of some known effects of substance P with bradykinin would be of interest.

In this paper we are going to summarize our results concerning the effects observed after intracerebral injection of bradykinin and the influence of this substance on various kinds of convulsions. In a parallel way the effects of substance P were checked in most experiments.

Bradykinin was prepared by the method of Rocha e Silva *et al.*[1] and Andrade *et al.*[2] As the standard preparation was not available, the activity of our preparation could not be expressed in units*. Therefore the doses are presented in milligrams. Our preparation caused contractions of the isolated guinea-pig ileum, in concentration of 10^{-4} – 10^{-5} and of the isolated rat uterus, in concentrations of 10^{-6} – 10^{-7} in the bath.

Substance P was prepared by the method of Pernow.[3] Standardization was not performed for the reason mentioned above. It was active on the isolated guinea-pig ileum in the concentration of 10^{-4} in the bath.

Intraventricular injections were performed on 8 cats. The cannulae were implanted in the lateral ventricle 3 – 7 days before the experiment, according to Feldberg and Sherwood,[4] using some technical modifications.[5] Doses of 50 mg bradykinin and 10 mg substance P were injected, dissolved in 0·5 ml. Tyrode solution. Bradykinin was injected intraventricularly also in mice, according to Haley's technique,[6] using an instrument for semi-automatic application.[7]

Action on Metrazol and Strychnine Seizure and on Electroshock

The median effective dose (ED_{50}) of metrazol was determined by the probit method of Litchfield and Wilcoxon[8] on mice. The positive reaction was a tonic extension of the hind limbs. Groups of 50 mice were used. The

* After the Meeting Prof. Rocha e Silva kindly performed in our Laboratory an assay and determined the potency of our preparation which was 0·1 unit per mg. We are most grateful to him.

first group was given only metrazol intravenously. To the second group 5 min before metrazol administration, a dose of 7 mg/20 g body weight of bradykinin was injected, which corresponds to 1/2 of the median lethal dose (LD_{50}) of our preparation. The third group was injected with 5 mg/20 g of substance P. This corresponds also to 1/2 LD_{50} of our preparation. The action of bradykinin and substance P on strychnine seizure and that of bradykinin on electroshock was examined by the same method. Electroshock was carried out by means of two electrodes fixed on the ears, using a sinusoidal current of 50 c/sec, and 0·2 sec duration. The resistance of the whole circuit including the animal was in every experiment carefully adjusted to 60 kΩ. The ED_{50} was expressed in volts.

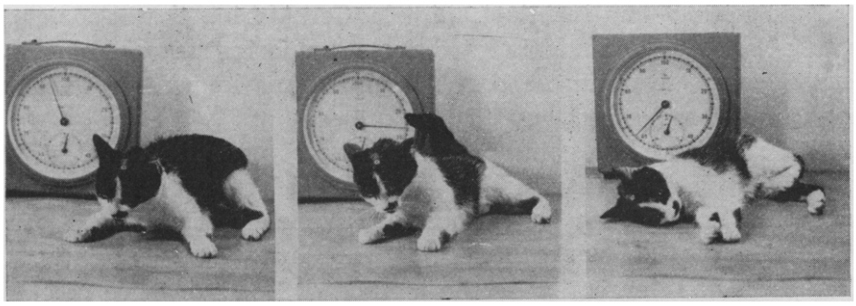

FIG. 1. The balance impairment 2 min after intracerebral injection of bradykinin.

After intracerebral injection of bradykinin within 1 min all cats miaouw. Muscular twiches beginning at the ears, move down the neck to dorsal muscles. The balance is impaired (Fig. 1). The cat falls to the side and cannot right itself. The forelegs are stretched with the claws outstretched. The hindlegs are under the body. In most cases, opisthotonus (Fig. 2) and convulsions develop. The animal may take bizzare positions. Autonomic symptoms are marked. Tachypnoea is always present from the first minutes after administration. The respiration is shallow, the frequency more than 100 per minute. The mouth is open, the tongue hanging out. Salivation is mostly present; micturition, and sometimes defaecation could be observed. Gradually, maximal mydriasis occurs (Fig. 3). Although the clinical picture was severe, all animals recovered and their behaviour and autonomic functions returned to normal after 60 – 90 min. With substance P some vegetative disturbances were observed, but the general behaviour was strikingly different, the animals making an impression of deep sedation.

Interesting were the results in mice. There is a clear picture showing an excitation of the central nervous system. The animals are very active, they run often to the left side (i.e. the side of injection). The move their

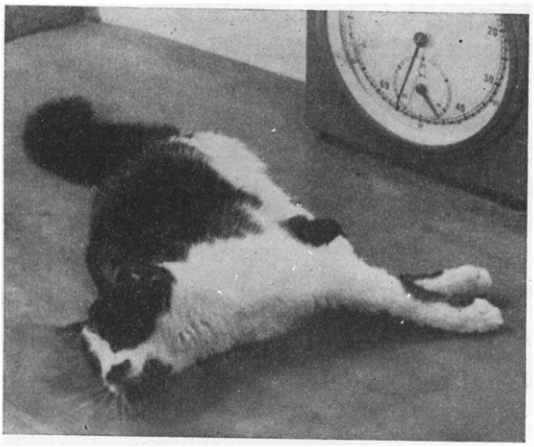

FIG. 2. Opisthotonus 12 min after intracerebral injection of bradykinin.

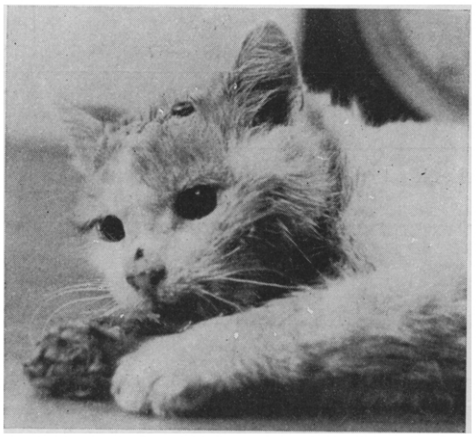

FIG. 3. Mydriasis 14 min after intracerebral injection of bradykinin.

tails and jump to remarkable heights. They may also have convulsions. A typical sign is piloerection so that they give the impression of a ball.[9]

As may be seen from Table I, bradykinin in the doses used decreases significantly the seizure threshold to metrazol, strychnine and electroshock induced convulsions, whereas, as known from the literature[10, 11, 12] and confirmed by us, substance P has the opposite effect.

Von Euler and Pernow[13] saw after intracerebral injection of substance P the same patterns with the predominant motoric sedation. Rocha e Silva[14] also described mydriasis in different experiments with bradykinin administred intraventricularly. As we have seen that our preparations, although of different provenience and purity, have the same effects as described by others, we may assume that also the newly described effects are reliable.

The action of bradykinin on smooth muscles and circulation is the object of main interest. These actions of both bradykinin and substance P are similar. In our experiments these peptides had an opposite effect. It seems to us, according to our results, that more attention should be paid to effects of bradykinin on the central nervous system directly, or to its interaction with drugs which influence the central nervous system.

TABLE I

The action of bradykinin and substance P on metrazol, strychnin and electroshock induced convulsions

Figures represent the relative changes in median effective dose (ED_{50}) in per cent with confidence limits (P = 0·05) after bradykinin or substance P pretreatment.

		Control	Bradykinin	Substance P
ED_{50}	metrazol	100	57·3 (49·0–67·0)	133·3 (115·7–153·3
	strychnin	100	59·0 (43·1–80·7)	131·4 (105·1–164·2)
	electroshock	100	83·7 (73·9–94·7)	—

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