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NEUROKININ FROM CEREBROSPINAL FLUID

III. Reciprocal actions with some drugs (1)

BY

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Drugs that modify the actions of pharmacologically actives polypeptides have been stiuded. KRIVOY (1957) described the preservation by LSD of the action of substance P in the guinea-pig ileum. KRIVOY and LANE (1962) studied the actions of several polypeptides on the dorsal roots potentials of the spinal nerves under the influence of LSD.

COLLIER and SHORLEY (1960) and COLLIER (1962) verified the antagonistic effects of antipyretic drugs related to the spasmogenic activity of bradykinin on the bronchiolar musculature.

WALASZECK, SMITH and HUGGINS (1962) carried out experiments concenred with the effects of possible drug antagonists on the arterial pressure and smooth muscle response to polypeptides.

On this report the influence of some drugs on the neurokinin action is studied.

MATERIAL AND METHODS

Rats were stunned by a blow on the head and bled to death. The duodenum proximate to the pylorus was immediately removed and placed in Ringer-Locke solution. A segment of duodenum were cut and carefully dissected away, tied at both ends with cotton thread. The muscle was mounted in a 3 ml chamber containing Ringer-Locke

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solution at 37° C, one end of each being secured to the bottom of the chamber and the other to a frontal lever that recorded the muscle movements on a smoked paper kymograph. A constant vigorous stream of room air was introduced in the chamber through a hypodermic needle.

Rats weighing 180-250 Gm were anesthetized by the intra peritoneal injection of sodium pentobarbital (130 mg/Kg). After tracheotomy, a small bore polyethylene tubing was introduced into the jugular vein, or the dorsal vein of the penis to permit the intravenous administration of the material to be assayed. Polyethylene tubing joined the carotid artery to recording manometer for registration of the arterial blood pressure. As an anticoagulant, 50 units of heparin in 1 ml of isotonic sodium chloride solution were injected intravenously.

Neurokinin was obtained from human cerebrospinal fluid incubated 15 minutes at 37° C with bovine globulin (NBC), and bradykinin (3 units/mg) from ox blood. Lysergic acid diethylamide (LSD) and Lysergic acid butanolamide (UML) "Sandoz", Sodium salycilate from New York Hospital Pharmacy, and hydrocortisone "Armour" were also used

Results

a) Influence of Lysergic acid derivatives :

The hypotensive effects of neurokinin and bradykinin, were enhanced with the previous administration of LSD (25 to 50 γ/Kg) and UML (250 to 1000/Kg). The same phenomenon was observed in the isolated rat duodenum. The Tables I, II, III and IV show the results obtained with the experiences carried out with neurokinin and lysergic acid derivatives on the duodenum and on the blood pressure of the rat.

Table I

Influence of LSD on the hypotensive action of neurokinin in rats .
($t = 2{,}96$; $P < 0.05$)

Dose of LSD (γ/kg)	Dose of NK (mg)	Hypotension in mm Hg	
		Before LSD	After LSD
25	12	22	26
25	18	18	36
50	30	18	80
50	30	14	38
50	30	24	62
	mean	19.2	48.4

TABLE II

Influence of UML on the hypotensive action of neurokinin in rats
($t = 4{,}38$; $P < 0.02$)

Dose of UML (γ/kg)	Dose of NK (mg)	Hypotension in mm Hg	
		Before UML	After UML
200	12	24	36
250	12	12	30
500	18	22	64
500	18	14	60
1000	20	28	76
	mean	20.00	53.21

TABLE III

Influence of LSD on the effect of neurokinin in the duodenum of the rat
($t = 5.46$; $p < 0.01$)

Dose of LSD (γ/kg)	Dose of NH (mg/ml)	Relaxation in mm	
		Before LSD	After LSD
0.01	1.66	20	21
0.015	0.66	50	70
0.03	0.33	8	24
0.03	1.66	47	70
0.03	1.66	32	63
0.03	1.66	30	47
0.03	2.00	35	62
	mean	31.71	51.00

TABLE IV

Influence of UML on the effect of neurokinin in the duodenum of the rat
($t = 7.97$; $P < 0.05$)

Dose of UML (γ/ml)	Dose of NK (mg/ml)	Relaxation in mm	
		Before UML	After UML
1.0	1.33	20	42
1.0	0.33	25	35
1.5	0.66	14	30
1.5	0.66	15	42
1.5	0.66	20	43
1.5	1.33	38	70
1.5	2.00	22	45
	mean	22.00	43.85

TABLE V

Inhibition of the hypotensive effect of neurokinin in rats by sodium salycilate
($t = 3.40$; $P < 0.02$)

Dose of Salycilate (mg/kg)	Dose of NK (mg)	Hypotension in mm Hg	
		Before Salyc.	After Salyc.
150	12	40	30
150	20	44	32
180	20	52	40
200	18	42	6
200	12	62	6
200	30	24	0
	mean	44.00	19.00

b) Influence of sodium salycilate and hydrocortisone :

Sodium salycilate and hydrocortisone inhibited the polypeptide effects on the rat blood pressure (TABLES V and VI) but not affected the hypotension produced by bradykinin.

The results obtained with experiments carried out on the rat duodenum were similar with those verified on the rat blood pressure. Sodium salycilate and hydrocortisone had an antagonistic effect related with neurokinin (TABLES VII and VIII) while did not inhibited bradykinin action.

TABLE VI

Inhibition of the hypotensive effect of neurokinin in rats by hydrocortisone
($t = 3,35$; $P < 0.05$)

Dose of HC mg/kg	Dose of NK (mg)	Hypotension in mm Hg	
		Before HC	After HC
50	20	16	0
50	12	28	8
50	20	36	8
100	20	16	0
100	20	88	10
100	20	46	10
	mean	38.33	3.6

When sodium salycilate was added to the bath produced marked relaxation of duodenum and the intestine only recovery the initial tonus after repeated whashes. Neurokinin was tested on the duodenum after salycilate, only when the muscle returned to the normal tonus.

TABLE VII

Inhibition of neurokinin in the rat duodenum by sodium salycilate
($t = 4.74$; $P < 0.01$)

Dose of Salycilate (mg/ml)	Dose of NK (mg/kg)	Relaxation in mm	
		Before salyc.	After salyc.
1.00	0.66	30	27
1.33	2.00	30	20
1.66	0.33	52	33
1.66	0.66	10	5
1.66	0.66	42	15
1.66	0.66	40	15
1.66	1.33	25	5
2.66	0.66	43	4
3.33	0.66	30	0
3.33	0.66	30	0
	mean	33.7	12.4

TABLE VIII

Inhibition of neurokinin in the rat duodenum by hydrocortisone
($t = 4.97$; $P < 0.01$)

Dose of HC (mg/ml)	Dose of NK (mg/ml)	Relaxation in mm	
		Before HC	After HC
0.083	1.66	40	40
0.166	1.66	42	14
0.166	0.66	45	17
0.166	2.00	38	19
0.166	2.00	40	15
0.166	0.66	38	14
0.166	0.66	20	10
0.166	0.66	40	15
0.373	0.66	40	13
0.333	0.66	40	7
	mean	38.3	27.9

Summary and Conclusions

1. — LSD and UML potentiated neurokinin effects on the duodenum and on the blood pressure of the rat.

2. — Sodium salycilate and hydrocortisone antagonized neurokinin on rat duodenum and blood pressure.

3. — Differences can be showed between neurokinin and bradykinin since first polypeptide is inhibited by sodium salycilate and hydrocortisone while the bradykinin effects were not affected by these drugs.

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