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Natriuretic Properties of [2-p-Ethylphenylalanine] deamino-6-carba-oxytocin (Nacartocin) in Cats

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Summary. Nacartocin, a synthetic analogue of oxytocin, [2-L-p-phenylalanine]deamino-6-carba-oxytocin has a specific natriuretic effect in cats. The doses of 0.05—10 μg/kg b.w. (0.05—10 nmols/kg) of Nacartocin applied i.v. caused a several fold increase in the excretion of sodium, while the excretion of kalium was only slightly enhanced.

Key words: Cat, natriuresis, Nacartocin

Introduction

Systematic studies of structure — activity relations led us to propose the synthesis of deamino-6-carba-oxytocin analogues with higher specific natriuretic activity (Hrbas et al., 1980a,b; Škopková et al., 1980; Barth et al., 1981; Lebl et al., 1982) in rats. In order to test their specific interaction with rat kidney membrane structures, we assayed the activation of adenylate cyclase by the analogues. In the series of analogues tested, [2-p-methylphenylalanine]deamino-6-carba-oxytocin and [2-p-ethylphenylalanine]deamino-6-carba-oxytocin (Butlen et al., 1983) had the highest binding affinity and activation ability. This accords with the finding that they had the highest natriuretic activity in the series of analogues tested. We chose [2-p-ethylphenylalanine]-deamino-6-carba-oxytocin (Nacartocin) for further studies. Although it had a lower ability of interaction than oxytocin in the membrane system of the human kidney medulla (Guillon et al., 1982), Nacartocin had a more specific natriuretic effect than [2-p-methylphenylalanine]deamino-6-carba-oxytocin. In order to obtain more information on the natriuretic action of Nacartocin, we investigated the effect of the peptide in experiments with cats.

Material and Methods

The experiments were performed on adult tom-cats weighing 1.84—3.4 kg. First, ether narcosis was used during the preparation of v. femoralis. A 1% chloralose solution was then applied i.v. (7—9 ml/kg). A canulla was inserted into a. femoralis for measurements of blood pressure. The urinary bladder was canullated and the orifice of the urethra was ligatured. An infusion of 10% manitol in 15 mM NaCl was administered into v. femoralis at a rate of 0.1 ml/min throughout the experiment. The mean blood pressure was registered by means of a Tesla LDP 102 apparatus. Urine samples were collected at 10 min intervals and their content of sodium, potassium and creatine was analysed

as described earlier (Lebl et al., 1980a). The conductivity of urine was recorded continuously. The doses were injected i.v. at a time when the urine flow and conductivity had remained constant for the three preceding 10 min intervals. The mean values of the three samples served as controls. The peptide analogue was applied in doses of 0.05—10 μg/kg body weight in a volume of 0.1 ml/kg. This dosage corresponds to the range of doses that elicit a medium natriuretic response in rats (Hrbas et al., 1980a).

Of the total number of 11 animals, one cat (no. 8) had to be excluded from the experiment due to bad health, and two had postoperation haematuria (nos. 1 and 9).

Results

Our dosage regimen allowed us to divide the results into three groups.

The lowest doses (0.05—0.1 μg/kg) of Nacartocin acted as threshold doses. As can be seen in Table 1, in half the cases the amount of excreted sodium increased (and the

Table 1 Excretion of urine, sodium, potassium and creatinine after the i.v. administration of Nacartocin to cats

Cat	Dose μg/kg	Duration of effect (min)	Urine volume, V ml/kg	%	$U_{Na}V$ μequiv/kg	%	U_KV μequiv/kg	%	$U_{Cr}V$ μg/kg	%
1	control	10	0.86	100	10.9	100	11.8	100	158	100
	10.0	40	2.68	78	126.8	292	78.9	167	939	145
2	control	10	1.93	100	127.6	100	47.0	100	308	100
	5.0	80	16.74	108	2040.3	200	361.7	96	2804	114
3	control	10	1.05	100	2.3	100	5.1	100	223	100
	5.0	40	2.43	57	54.0	581	53.2	259	1016	114
4	control	10	1.10	100	57.7	100	10.9	100	216	100
	5.0	80	10.60	120	1229.7	267	156.2	179	2028	117
5	control	10	1.01	100	23.0	100	31.7	100	258	100
	0.5	120	14.0	116	1163.4	422	439.4	115	1370	44
7	control	10	2.34	100	5.1	100	7.7	100	213	100
	0.05	120	8.33	30	270.2	444	201.2	218	2723	107
9	control	10	0.56	100	5.7	100	12.6	100	245	100
	0.1	40	2.26	101	17.8	78	51.5	102	916	93
	0.5	100	5.87	105	82.8	145	255.7	203	2447	100
	10.0	50	4.48	160	399.2	1401	261.8	416	1499	122
10	control	10	0.55	100	9.0	100	20.7	100	217	100
	0.05	120	8.00	121	391.8	363	308.8	124	3437	132
	0.5	60	3.90	118	430.6	798	190.0	153	1317	101
	10.0	60	4.24	128	538.7	998	165.4	133	1118	86
11	control	10	0.40	100	3.8	100	42.0	100	250	100
	0.05	80	1.80	56	19.3	63	311.7	93	1878	94
	0.5	70	1.56	56	81.5	306	309.5	105	1798	103
	6.6	30	1.00	83	117.8	1033	197.8	157	961	128

rate of urine flow decreased in nos. 7 and 11). In one case (no. 7), the amount of excreted potassium increased. The other parameters were not influenced by these doses.

Nacartocin in doses of 0.5 μg/kg led to a pronounced natriuretic response, in some cases eight times higher than the basic level. In one case, which had the lowest natriuretic response, increased potassium excretion was observed (no. 9).

The highest doses (5—10 μg/kg) were distinctly natriuretic, resulting in 2—14 times higher sodium excretion. We should like to point out that the relatively lowest natriuretic effects were observed in cases that had had high basic sodium excretion before the application of Nacartocin. In both cases (nos. 2 and 4), the absolute values of sodium excretion were highest. The increase in sodium excretion was accompanied by a slight increase in potassium excretion, the ratio remaining in favour of sodium excretion. Creatinine excretion also increased slightly, on the average by 10—20%, in one case by 50%.

Discussion

The cumulation of modifications in the N-terminal part of the oxytocin molecule specifically increased the natriuretic activity of the resultant analogue [2-p-ethylphenylalanine]deamino-6-carba-oxytocin (Machová and Jošt, 1975, Lebl et al., 1982). In our previous experiments with rats, in which we determined the influence of Nacartocin on natriuresis and haemodynamic parameters, we observed a selective increase of natriuresis that was caused by the increased tubular rejection of sodium (Barth et al., 1983).

The present study confirmed the selective character of the natriuretic action of Nacartocin. A tenfold increase of sodium excretion documents the efficacy of the compound. The concurrent slight increase in the amount of creatinine excreted indicates the possible inhibition of tubular sodium resorption. The slight diuretic effect of the highest doses of Nacartocin can be explained by the osmotic action of the increased amount of electrolytes excreted.

The results of our experiments with cats can be said to confirm that the analogue of oxytocin has natriuretic activity, as had been observed in rats.

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