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Bioavailability of Carbetocin ([2-*O*-methyltyrosine] deamino-1-carba oxytocin) in the rat

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Introduction

The long-acting synthetic analog of oxytocin (OXT), Carbetocin ([2-*O*-methyltyrosine]-deamino-1-carba oxytocin) (CE), becomes a drug of choice in veterinary medicine, particularly for reproductive purposes.

Results and Discussion

OXT and CE [1] were synthesized at the Institute of Organic Chemistry and Biochemistry. Tritiated CE was prepared as described earlier [2]. Uterotonic and galactogogic tests were performed as previously described [3]. The half-life was determined as described in Ref. 4.

Comparison of intravenous (i.v.) and intranasal (i.n.) application of OXT and CE is shown in Figs. 1A–D. To obtain a measurable effect after i.n. application a dose of OXT 4 orders of magnitude higher than that used for i.v. administration was required, but with CE, the i.n. dose needed was only 2 orders of magnitude higher than the i.v. dose. The time-course of response to both peptides applied i.n. resembled that of CE after i.v. administration.

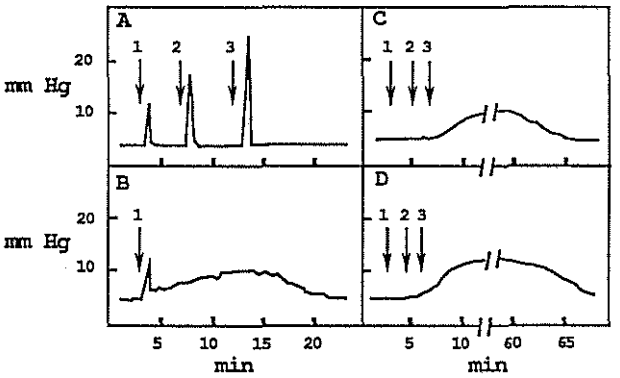

Fig. 1. Intramammary pressure in lactating rats after i.v. (A,B) or i.n. (C,D) administration of OXT (A,C) or CE (B,D). (A) 1: 2.75×10^{-7} mg, 2: 5.5×10^{-7} mg, 3: 1.1×10^{-6} mg; (B) 1: 4×10^{-5} mg; (C) 1: 2×10^{-4} mg, 2: 2×10^{-3} mg, 3: 2×10^{-2} mg; (D) 1: 1×10^{-4} mg, 2: 1×10^{-3} mg, 3: 1×10^{-2} mg.

The half-life of CE determined in plasma of female rats in induced estrus after i.v. injection of radioactive CE (5×10^5–1×10^6 cpm) in six experiments was 8.1 min. A similarly enhanced value was found for deamino-dicarba-OXT (7.8 min) [4], whereas for OXT the value was ca. 4 min.

Penetration of CE into the blood stream was investigated using tritiated CE as a tracer. We followed the rate at which the radioactivity appeared in plasma after i.n. application and the time course of the galactogogic effect. The radioactive compounds appeared in plasma 2.5 min after application, and the plateau level was reached in 10 min. After this time, the radioactivity in plasma increased only very slowly (Fig. 2). The rate of absorption was relatively high and coincided with the appearance of biological effect. However, the galactogogic response disappeared from the plasma at a faster rate than the radioactivity.

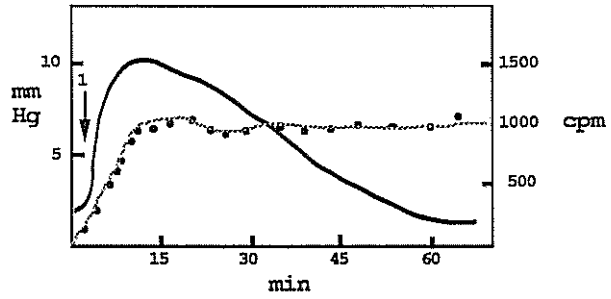

Fig. 2. Time-courses of the intramammary pressure (——) and the radioactivity (●—●) in plasma of a lactating rat after i.n. administration of tritiated CE. 1-CE (2.5×10^{-3} mg + 1 μCi of the tritiated compound) was given in a volume of 20 μl.

Tritiated CE (4×10^{-5} mg) was administered subcutaneously to lactating female rats to establish its distribution among tissues and its possible passage into the young rats via feeding. The lactating rats were killed after 24 h and their young 24 or 48 h after peptide administration. Radioactivity was determined in blood, kidneys, liver, brain, reproductive organs and milk tissue. The highest radioactivity was found in kidneys of lactating rats, as well as of their young and in the liver (about half of the amount in kidneys).

References

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