

ROLE OF SPINAL PITUITARY ADENYLATE CYCLASE ACTIVATING POLYPEPTIDE (PACAP) IN THE CONTROL OF LOWER URINARY TRACT IN RATS WITH SPINAL CORD INJURY

Aims of Study

Pituitary adenylate cyclase activating polypeptide (PACAP) is a 38 amino acid brain-gut peptide, which is a member of the secretin/glucagon/vasoactive intestinal polypeptide (VIP) family. The amino acid sequence of PACAP has a 68% homology to that of VIP and is the same in sheep, rat and human. Various observations have implicated these peptides in the neural control of bladder function. Immunohistochemical experiments identified PACAP- and VIP-containing nerve fibers projecting to the sacral parasympathetic nucleus. Large doses of VIP (1-10 µg) injected intrathecally (i.t.) inhibited bladder activity in normal cats, whereas smaller doses of VIP (0.1-1 µg i.t.) facilitated bladder activity in chronic spinal cats [2]. Thus, the spinal actions of VIP were altered by spinal cord injury. It was also shown that i.t. injection of PACAP-27 in normal, conscious rats facilitated reflex bladder activity [1]. The present experiments were undertaken to determine whether the effect of PACAP on bladder activity were also changed after spinal cord injury. The effects of PACAP-38 (0.1-30 µg i.t.) on the micturition reflex were evaluated in decerebrate, unanesthetized chronic spinal as well as spinal intact rats.

Methods

Experiments were performed on female Sprague-Dawley rats (200-300 g) under unanesthetized conditions following decerebration. All surgical procedures were performed under halothane anesthesia. A transurethral bladder catheter connected to a pressure transducer was used to record bladder pressure under isovolumetric conditions or during continuous infusion cystometry with physiological saline (0.21 ml/min). In all animals during isovolumetric recording, the ureters were tied distally, cut and the proximal ends cannulated (PE-10) and drained externally. In some rats, the hypogastric nerves (HGN) were sectioned bilaterally to eliminate the major sympathetic input to the bladder. An intrathecal (i.t.) catheter (PE-10) was inserted through a slit in the atlanto-occipital membrane and passed caudally to the L6-level of the spinal cord. The volume of fluid within the catheter was kept constant at 6 µl in all animals. Twenty-four rats were spinalized at T8-9 under halothane anesthesia. The bladders of spinal rats were expressed manually 2 or 3 times daily. The experiments on spinalized rats were performed 2 to 4 weeks post-spinalization. In spinalized rats, an i.t. catheterization was performed after a T11-12 laminectomy. For decerebration, animals were anesthetized with halothane (2%, in oxygen) during surgery. Both carotid arteries were ligated to reduce bleeding during the decerebration procedure. After a craniotomy, a precollicular decerebration was performed using a blunt spatula. Experiments were performed 2 to 8 h post-decerebration.

Results

- (1) Under isovolumetric conditions in chronic spinal rats with HGNs-intact PACAP (10 µg) depressed (range: 6-90 %) bladder contraction amplitude; whereas 30 µg enhanced (range: 150-200 %) the amplitude. However, in some experiments (57 %) the effects of PACAP were biphasic consisting of excitation followed by inhibition (range: 20-75 % change). The effect of PACAP appeared 1-3 min after injection and persisted for 20-80 min.
- (2) Under isovolumetric conditions in chronic spinal rats with HGNs-transected PACAP commonly increased bladder contraction amplitude (range: 5-200 % by 10 µg and 58-566 % by 30 µg).
- (3) During continuous infusion cystometrograms (CMGs) in chronic spinal rats with HGNs-intact or -transected PACAP in doses of 10 and 30 µg i.t. decreased reflex rhythmic bladder contraction amplitude (range: 31-100 %).
- (4) During continuous infusion CMGs in spinal cord intact rats with either HGNs-intact or -transected PACAP (10-30 µg i.t.) exhibited mixed effects. A biphasic effect (initial excitation followed by inhibition) occurred after a high dose with HGNs-intact; whereas with HGNs-transected a facilitatory effect of 10 µg dose was seen. The effect of the large dose (30 µg) was not changed by HGN transection.
- (5) In spinal cord intact rats with either HGNs-intact or -transected under isovolumetric conditions, it was impossible to maintain consistent rhythmic bladder activity (n=10) and therefore studies could not be conducted.
- (6) When PACAP completely blocked reflex bladder activity during continuous infusion CMGs, fluid

continually leaked from the bladder (i.e., overflow incontinence).

Conclusions

- (1) In chronic spinal rats with HGNs-transected, PACAP stimulates spinal parasympathetic pathways and facilitates bladder contractions.
- (2) In chronic spinal rats with HGNs-intact, PACAP also stimulates sympathetic pathways to the bladder and can suppress bladder contractions.
- (3) Lack of facilitation by PACAP of bladder contractions during continuous CMGs, is most reasonably attributed to inhibition (or relaxation) of the urethral outlet (urethral sphincter and/or smooth muscle) since overflow incontinence occurred with only a small increase in intravesical pressure.
- (4) It is concluded that PACAP can activate spinal circuitry to facilitate the autonomic outflow to the urinary bladder.

References

1. Neuroscience 66:1009-1014, 1995.
2. J Auton Nerv Syst 30 Suppl:S71-77, 1990.