Involvement of Central GABA Receptors in the Regulation of the Urinary Bladder Function of Anaesthetized Rats

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Summary. Cystometric recordings were performed in pentobarbitone anaesthetized rats and the effects of gammaaminobutyric acid (GABA) mechanisms on urinary bladder function were evaluated as their influence on a bladder hyperactivity induced by 1-dihydroxyphenylalanine (L-DOPA) after peripheral decarboxylase inhibition. The bladder response was inhibited by intracerebroventricular (i.c.v., 4th ventricle) injections of GABA (250 μg), muscimol (0.2 μg) and glycine (1,000 μg) as well as by systemically administered muscimol (4 mg/kg) and diazepam (2 mg/kg). Intravenous (i.v.) bicuculline, but not i.v. strychnine, antagonized the inhibitory actions of intraperitoneal (i.p.) and i.c.v. muscimol and i.v. diazepam while the opposite was true for the inhibitory action of i.c.v. glycine. In rats not pretreated with L-DOPA, i.p. administration of bicuculline (4 mg/kg) after 15 min caused prominent detrusor contractions that were prevented by an infracollicular brain transection.

It is suggested that GABA synapses in the pontine-mesencephalic brain region may be involved in the modulation of urinary bladder function.

Key words: L-DOPA — GABA — Muscimol — Urinary bladder.

Introduction

A considerable amount of evidence suggests an inhibitory neurotransmitter role for gammaaminobutyric acid (GABA) and glycine in mammalian central nervous system (Curtis and Johnston, 1974; Krnjevic, 1974; de Feudis, 1975). Based on clinical (Kiesswetter, and Schober, 1975; Kiesswetter, 1978; Madersbacher, 1978) and experimental (Teague and Merrill, 1978) studies with baclofen, a structural GABA analogue, it has been suggested that spinal GABA mechanisms are involved in regulation of urinary bladder function.

Recently we have shown that administration of the catecholamine precursor L-DOPA after peripheral decarboxylase inhibition results in a hyperactive bladder response, probably elicited from dopaminergic structures in the mesencephalic-pontine region of rat brain (Sillén et al., 1979; Sillén et al., submitted).

The present experiments were undertaken to examine the supraspinal influence of GABA mechanisms on the above mentioned hyperactive urinary bladder response in the rat. Since GABA passes poorly through the blood brain barrier (Kuriyama and Sze, 1974) and since the gabaergic properties of baclofen have been questioned (for ref., see Koea, 1978) we have used muscimol, considered the best GABA analogue available (for ref., see Enna and Magge, 1979) and diazepam, many actions of which are due to GABA receptor activation (Costa et al., 1975; Hafely et al., 1975; Curtis et al., 1976).

Methods

Male Sprague-Dawley rats (180 — 250 g) were used in all experiments. Cystometric recordings were performed in rats anaesthetized with pentobarbitone (60 mg/kg i.p.). For this purpose a catheter was inserted into the bladder through an incision in the proximal urethra. Saline was infused at a constant rate of 2.0 — 3.3 ml/h into the bladder and the intravesical pressure recorded via a Statham pressure transducer (P23Dc) writing on a Grass Polygraph (for further details, see Sillén et al., 1979). Simultaneously, in some rats the intraduominal pressure was recorded on a Grass Polygraph via a catheter (Portex, PP50) implanted into the abdominal cavity just prior to bladder experiments.

Intracerebroventricular catheters (Portex, PP25) were implanted into the 4th cerebral ventricle as described by Gomes et al. (1978). Briefly the membrana atlanto-occipitalis was exposed by a midline incision of the neck muscles and an angular catheter (90 — 110°) was
Effects of Systemic and i.e.v. Administration of GABA, Bladder Hyperactivity

The influence of GABA and glycine on urinary bladder regulation was evaluated as their influence on a centrally elicited hyperactive bladder induced by L-DOPA. Treatment with carbidopa (100 mg/kg i.p.) and L-DOPA (100 mg/kg i.p., 15 min after carbidopa) resulted within 15 min in prominent detrusor contractions that remained stable for at least 120 min (for further details, Sillén et al., 1979).

GABA. Intracerebroventricular administration of GABA (threshold dose: 250 μg, n = 6) completely but transiently suppressed the L-DOPA induced bladder hyperactivity. When GABA was given in cumulative doses (250–2,000 μg) the duration of the inhibition was prolonged in a dose-dependent manner (Fig. 1). Treatment with i.p. GABA in considerably higher doses (750 mg/kg, n = 4) had no effects on detrusor contractions after L-DOPA. To exclude that the effects of i.e.v. GABA were due to generally unspecific actions, such as local anaesthetic or osmotic properties of GABA, lidocaine (180 μg, n = 3) or sucrose (1 mg, n = 3) was administered i.e.v. to some rats. These treatments as well as i.e.v. (10 μl, n = 3) and i.p. (10 ml/kg, n = 3) NaCl had negligible effects on the hyperactive bladder after L-DOPA compared to the inhibitory actions obtained in the same rats 10 min before by i.e.v. GABA.

Muscimol and Diazepam. Pretreatment with i.p. muscimol 4 mg/kg, (n = 5, 5 min before carbidopa, Fig. 1) completely prevented the hyperactive bladder response to L-DOPA in all rats for at least 30 min. After a lower dose of muscimol 2 mg/kg (n = 4), a complete inhibition was seen in 2 out of 4 rats. A total inhibition of the detrusor contractions was also obtained by i.e.v. muscimol, when this agent was administered during maximal L-DOPA response. After muscimol 0.1–0.2 μg (n = 10, 25–30 min after L-DOPA, Fig. 1) the inhibition occurred in all rats, whereas with a lower dose 0.05 μg the response was inconsistent (2 out of 4). The inhibition after 0.1–0.2 μg occurred within 1 min and lasted for at least 30 min.

Following diazepam (2 mg/kg i.p., n = 6, 25–30 min after L-DOPA), the depression of detrusor contractions developed more slowly but complete inhibition of the L-DOPA induced hyperactivity was always seen after 5 min, and lasted for 10–25 min.

Glycine. When given 30 min after L-DOPA, i.e.v. glycine (1,000 μg, n = 8) completely suppressed the detrusor contractions in all rats for at least 30 min. After glycine 500 μg the results were inconsistent (n = 4).