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BIPHASIC EFFECT OF APOMORPHINE, AN ANTI-PARKINSONIAN DRUG, ON BLADDER FUNCTION IN RATS

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Abstract—The effects of anti-parkinsonian drugs on bladder function have been controversial; namely, some aggravated while others alleviated bladder dysfunction in patients with Parkinson disease. These studies, however, did not consider the dose- and time-dependent effects. Therefore, we investigated these effects of apomorphine, an anti-parkinsonian drug and a nonselective dopamine receptor agonist, on the bladder function using normal conscious rats. Consecutive cycles of micturition were analyzed for 30-min periods before and after (over a 4-h period) s.c. administration of a single dose of 0.01 (low), 0.05 (medium), 0.5 (high) mg/kg of apomorphine or saline to the rats. Apomorphine administration produced various effects in relevant urodynamic parameters, although the monitored parameters remained unchanged in saline-administered rats. During filling, low-dose apomorphine induced initial decreases in voiding frequency (VF; defined as the number of voidings during a 15-min period). However, medium- and high-dose apomorphine dose-dependently induced initial increases in VF, and was followed by decreases in VF. These doses also induced initial increase in threshold pressure. During voiding, low-dose apomorphine induced initial increases in micturition volume (MV), which reflected an increase in bladder capacity (BC). However, medium- and high-dose apomorphine dose-dependently induced initial decreases in MV, and was followed by increases in MV. These doses also dose-dependently induced an initial increase in maximum bladder contraction pressure during the early phase after administration. The present study demonstrated that apomorphine displayed a dose- and time-dependent biphasic effect on the normal bladder filling function. These pharmacodynamic characteristics of apomorphine could be applicable to other anti-parkinsonian drugs such as levodopa and nonselective dopamine receptor agonists, and may account for the previous reported conflicting effects of anti-parkinsonian drugs on bladder dysfunction in patients with Parkinson disease, although it needs to be evaluated in disease status.

Key words: bladder, lower urinary tract, urodynamics, apomorphine, Parkinson disease, dopamine.

Bladder function is regulated by a reciprocal mechanism comprising filling–voiding phases, where each phase is independently modulated by various drugs. In patients with Parkinson disease (PD), levodopa and dopamine receptor agonists are the standard drugs for the treatment of motor disturbance, however the effects of these anti-parkinsonian drugs on bladder function remain unclear to date. Previous clinical reports have indicated that both levodopa and apomorphine are not specific and display a higher affinity for dopamine D2 receptors in aggravating and alleviating bladder filling dysfunction in PD patients. As a result, the clinical outcomes/effects of these drugs on bladder dysfunction are controversial (Aranda et al., 1983; Christmas et al., 1988; Fitzmaurice et al., 1985) and remain unresolved as yet. Previous experimental studies have demonstrated that anti-parkinsonian drugs (such as levodopa and most dopamine receptor agonists) uniformly decrease voiding interval and micturition volume (MV) (Ishizuka et al., 1995; Kontani et al., 1990; Sillen et al., 1979, 1981, 1982) by activating the dopamine D2 receptors having the opposite effect on the inhibition-mediating dopamine D1 receptors in normal and PD models (Seki et al., 2001; Yoshimura et al., 1993, 1998, 2003). However, these experimental findings incompletely have accounted for the clinically controversial effects. On the other hand, there are some interesting clinical and experimental reports showed that levodopa and dopamine receptor agonists exhibit biphasic effects on movement (Martin and Bendesky, 1984), cardiovascular function (Nakayama et al., 2001; Paalzow and Paalzow, 1986) and pain (Paalzow, 1992), in a dose- and time-dependent manner, and that non-selective dopamine D1/D2 agonists and D2 agonists also exhibit biphasic effects on ejaculatory, erectile responses and copulation in male sexual function in a dose-dependent manner (Peeters and Giuliano, 2008). Interestingly, Benson et al. (1976) have indicated two clinical cases where bladder capacity is increased with low-dose administration of levodopa, and decreased with high-dose administration. Recently, we also had experience with a de novo PD patient whose bladder capacity decreased 1 h after 100 mg

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Abbreviations: BC, bladder capacity; DCI, decarboxylase inhibitor; MP, maximum bladder contraction pressure; MV, micturition volume; PD, Parkinson disease; PVR, postvoid residual; TP, threshold pressure; VF, voiding frequency.

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levodopa/decarboxylase inhibitor (DCI) taken orally, and increased about 5 h after that (data not reported).

Therefore, we assumed that a failure to fully consider the dose and time effects in the experimental model may have led to the difficulties explaining the complex clinical effects that are observed, and investigated dose- and time-dependent effects of a single dose of apomorphine (as a non-selective dopamine receptor agonist) on bladder function in normal, conscious and non-restrained rats.

EXPERIMENTAL PROCEDURES

Animals

Experiments were performed on 30 adult male Sprague–Dawley rats (12–14 weeks old, weighing 250–350 g) in accordance to the Chiba University Guideline for the Care and Use of Laboratory Animals. The experimental protocol was approved by the Animal Ethics Committee, Chiba University Graduate School of Medicine. All efforts were made to minimize animal suffering and reduce the number of animals used. Animals were accommodated in a room under standard environmental conditions with an alternating 12-h light/dark cycle.

Surgical preparation

Under general anesthesia with Nembutal (40 mg/kg i.p.), a polyethylene catheter (PE-50; Natsume Co. Ltd., Tokyo, Japan) was implanted in the bladder through the dome exposed by a midline abdominal incision (Malmgren et al., 1987; Seki et al., 2001). The catheter was tunneled s.c. and the orifice was dorsally positioned on the back of animals. Antibiotic (mycillin, 0.05 ml/kg i.m.; Kawasaki Mitaka Pharmaceutical Co. Ltd., Tokyo, Japan) was used for 2–4 days postoperatively. At 2–4 days after fixation of the catheter, animals were housed individually in metabolic cages and were harnessed such that fluid access to the bladder could be realized via an external tube connected to the catheter.

Urodynamic evaluation

After acclimatization (1–2 days) in the metabolic cages, urodynamic evaluations of the rodents were performed in the evening without anesthesia or restraint. The bladder catheter-fitted external tube was connected to a pressure transducer (Urolab Micro, Life-tech Inc., Tokyo, Japan) and an infusion pump (KDS-101, KDScientific Inc., Tokyo, Japan) via a T-tube. Saline at room temperature was infused into the bladder at a rate of 12 ml/h. Voided urine volume was collected and measured using an electronic scale (A&D Inc., Tokyo, Japan). Real-time intravesical pressure and voided volume were symmetrically recorded continuously with time (PowerLab, ADInstruments, Tokyo, Japan). Consecutive cycles of micturition monitored at 5–15 min intervals were analyzed for 30 min before and over a 4 h period after saline or drug administration. The monitored urodynamic parameters included voiding frequency (VF; defined as the number of voiding during a 15-min period), MV, threshold pressure (TP) and maximum bladder contraction pressure (MP). The TP was defined as last intravesical pressure just before starting bladder contraction for voiding, and bladder contraction pressure as intravesical pressure during voiding.

Drug administration

In this study, apomorphine was used as anti-parkinsonian drug and non-selective dopamine receptor agonist, because apomorphine had been well-used both in clinical and urogenital experimental studies, and easy and less-invasive administration was favorable.

After establishing equilibration with 30–60 min baseline recording, a single low (0.01), medium (0.05), and high (0.5) dose (mg/kg) of apomorphine (Sigma Inc., Tokyo, Japan), or saline (vehicle) was administered s.c. to the rats (n=7, 7, 8, and 8, respectively). Doges of apomorphine were determined according to the clinical usual dose (0.05 mg/kg). Low dose was 1/5 of the usual dose and a high dose is 10-fold the usual dose.

Statistical analysis

All data values are expressed as the mean±standard error (SE). Commercially available software (Excel Statistics Ver 6.0; Esumi Inc., Tokyo, Japan) was used for statistical analysis. Statistical comparisons were performed by repeated measures of variance (ANOVA) with subsequent individual comparisons by the Fisher's protected least significant difference test or paired t-test. Differences where $P<0.05$ were considered statistically significant.

RESULTS

Effects of a single dose of apomorphine on VF (Fig. 1)

Compared with the baseline assessment, VF did not significantly change with saline administration. However, low-dose apomorphine (0.01 mg/kg) tended to monophasically decrease VF (30–105 min) for a short period of time during the early phase after administration (with certain time points showing significant ($P<0.05$) differences when compared with saline-treated values). At medium (0.05 mg/kg) and high (0.5 mg/kg) doses, apomorphine indicated a biphasic action; increasing VF (15–75, 15–120 min) for short durations in the early phase, followed by slight decreasing VF (150–165, 180–240 min) for longer durations during the late phase after administration, respectively. Note that the dose-dependent effects were significantly ($P<0.05$) different from controls at certain time-points.

Effects of a single dose of apomorphine on MV (Fig. 2)

Compared with the baseline, MV did not indicate any significant changes with saline administration. However, low-

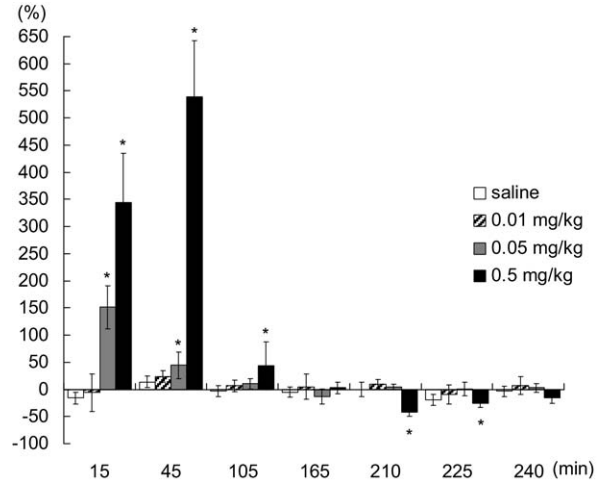

Fig. 1. Effects of apomorphine on the VF after s.c. administration of 0.01 (n=7), 0.05 (n=7) and 0.5 (n=8) mg/kg were monitored for 4-h. Animals administered with saline were treated as controls (n=8). The changing rate (%) was normalized by dividing the data after drug administration minus the baseline data before that by the baseline data before that and multiplying by 100. Values are expressed as the mean±standard error (SE). Differences (vs. saline-administrated group) where $P<0.05$ (*) were considered statistically significant.