POLY- AND DI-PHLORETTIN PHOSPHATE-INDUCED ALTERATIONS ON DIURESIS AND ANTIDIURESIS IN RESPONSE TO INTRACEREBROVENTRICULAR PROSTAGLANDIN A₂

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It has been demonstrated that when prostaglandin (PG) E₁ is infused into the 3rd ventricle, water diuresis is inhibited (1) and we found that PGA₂, when injected intracerebroventricularly (i.c.v.), increased urine outflow in 15 out of 26 rats and decreased it in the remaining animals. Thus, these effects appeared to be central in origin and suggested two quite different action-sites for PGA₂ which were characteristic of an individual rat (2). On the other hand, it is well known that polyphloretin phosphate (PPP), a polyanionic polyester of phloretin and phosphoric acid is a specific and competitive antagonist on certain peripheral actions of PGE₂ and PGF₂α (3-5). In the present work we attempted to determine whether or not i.c.v. administered PPP and its related compound, diphloretin phosphate (DPP) also altered the centrally-mediated diuretic and antidiuretic effects of i.c.v. PGA₂.

Detailed methods have been described elsewhere (6). Briefly, male Wistar rats (280-300 g) were anaesthetized with ethanol given p.o. and an i.v. infusion of 3 % ethanol (0.1 ml/min) was given to maintain anaesthesia and diuresis. The ventricular system from the ventricular lateralis to the aquaeductus cerebri was perfused with artificial cerebrospinal fluid (CSF) at a rate of 10 μl/min. PGA₂ was injected at a volume of 10 μl through a ventricular cannula. The bladder was catheterized and urine outflow was recorded by a photoelectric drop counter. Blood pressure was also recorded through a cannula inserted into the carotid artery. PGA₂, PPP and DPP were provided by Ono Pharmaceutical Co., Ltd., Osaka. As described previously (2), PGA₂ was dissolved immediately before use by absolute ethanol and diluted by the CSF to give a concentration of 10 nmoles/10 μl (ethanol concentration; 3 %).

It has been reported that the increase and decrease in urine outflow by i.c.v. injections of 10 nmoles of PGA₂ were about 30 % and 34 % for 40 min, respectively, and the diuretic and antidiuretic responses were reproducible in the same animals in repeated experiments (2). Consequently, in the present work, the effect of i.c.v. PGA₂ was tested and the control CSF for the i.c.v. perfusion was replaced by CSF containing PPP at 13 μM or DPP at 0.27 mM. Sixty min after start of the perfusion with PPP or DPP, PGA₂ was again injected i.c.v. at the same dose.

In rats with a diuresis produced in response to PGA₂, this was reversed to antidiuresis
FIG. 1. Effects of i.c.v. PGA₂ in the presence of PPP or DPP on urine outflow in rats in which diuresis (upper panels) and antidiuresis (bottom panels) occurred in response to PGA₂ alone. Ordinate; urine outflow (pre-PGA₂ outflow, 0.8-1.2 ml/10 min as 100%), abscissa; time (min) after the i.c.v. injection of 10 nmoles of PGA₂. PGA₂ was injected 60 min after starting the perfusion with 10 μM PPP or 0.27 mM DPP at the rate of 10 μl/min. Bars indicate S.E. in 8-10 animals. Time-courses for diuretic and antidiuretic effects of PGA₂ alone have already been presented elsewhere (2).

when PGA₂ was injected during the PPP-or DPP-perfusions (Fig. 1). On the other hand, in other rats with an antidiuresis in response to PGA₂ alone, PPP did not alter the antidiuretic effect of PGA₂ but to some extent, DPP prevented the antidiuretic effect of the PG (no significant difference between the PGA₂ -DPP- and DPP-treated groups).

The present evidence also suggests that in rats with a diuresis after PGA₂, antidiuretic mechanisms are apparently inferior to diuretic mechanisms in response to PGA₂ and PPP which did not influence the antidiuretic action-sites antagonized the diuretic response to PGA₂. Therefore, it appears that the antidiuretic mechanism of PGA₂ was indeed unmasked by PPP and that the developments of both effects were independent of each other. In the rat in which PGA₂ alone was the antidiuretic, DPP inhibited the antidiuretic response to PGA₂. However, the diuretic effect of PGA₂ was reversed to one of antidiuresis during the perfusion with DPP, thus this reversed antidiuresis was not prevented by DPP.

PPP and DPP at the doses perfused did not alter urine outflow and blood pressure and PGA₂, PGA₂+PPP and PGA₂ + DPP in doses given herein had no effect on the blood pressure. It would appear that these effects of PGA₂ with/without PPP or DPP were not directly related with change in blood pressure.
The pharmacological character of the action-sites for the diuretic effect of PGA₂ in the
brain is probably similar to that of peripheral receptors, since PPP, the potent inhibitor of
certain peripheral actions of the PGs prevented the development of diuresis in response to
i.c.v. PGA₂.

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DIFERENTIAL INOTROPIC-CHRONOTROPIC ACTION
OF CARTEOLOL

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Adrenergic beta-receptor blocking agents are roughly divided in two groups such as
DCI and pindolol, or propranolol on the presence or absence of sympathomimetic effects.
It has been reported that a newly synthesized beta-blocker, carteolol (dl-5(3-tert-butilamino-
2-hydroxy) proxy-3,4-dihydrocarbostyril hydrochloride), is 10–30 times more potent than
propranolol, and in higher doses has sympathomimetic properties (1–3). In the present
study, the sympathomimetic effects of carteolol on heart rate and contractility were in-
vestedigated, using the isolated, blood-perfused dog atrium preparation (4, 5).

Nine adult mongrel dogs of either sex weighing from 12 to 16 kg were anesthetized with
sodium pentobarbital, 30 mg/kg, i.v.. The isolated right atrial muscle was perfused with
arterial blood through a cannulated sinus node artery. The blood was fed from a carotid
artery of a heparinized support dog under constant perfusion pressure of 100 mm Hg by aid
of a peristaltic pump (Harvard Apparatus 1210). The sinus rate and isometric tension
development of the atrium were continuously recorded. Details of the preparation were
reported in previous papers (4, 5).

When an adequate dose of carteolol was injected into the cannulated sinus node artery
of the isolated atrium, positive chronotropic and inotropic effects were induced. As
carteolol-induced chronotropic and inotropic effects were long-lasting, cumulative doses
were applied in all experiments. The threshold dose for inducing positive effects was ap-
proximately 0.3 µg. When 0.01–0.03 µg of norepinephrine was administered into the
sinus node artery, prominent positive chronotropic and inotropic effects were induced (5–7).