Contribution of prostaglandins to the vasodepressor effect of dopamine in the rat

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There is general agreement that the administration of dopamine causes reduction of blood pressure in animals pre-treated with α-adrenoceptor blocking agents (Goldberg, 1972); this hypotensive response is thought to be due to vasodilatation of the renal, mesenteric and coeliac beds (Eble, 1964).

Such a vasodepressor effect is not due to the stimulation of vascular β-adrenoceptors, since (±)-propranolol was not able to block it. Moreover, inability of pretreatment by reserpine, monoamine oxidase inhibitors, atropine or antihistamines to attenuate the vasodepressor action of dopamine, and specific antagonism for this effect by several phenothiazines, haloperidol and other butyrophenones suggest that dopamine causes vasodilatation by an unusual mechanism: stimulation of specific vascular receptors (Goldberg, 1975).

Nevertheless the release by dopamine of other vasodepressor agents, such as endogenous prostaglandins (PG) could also explain the depressor effect of the amine, since PG, and particularly PGA_1, mimic some effects of dopamine.

Based on this hypothesis, we investigated the effect of indomethacin, a potent inhibitor of PG synthesis and release, on the vasodepressor action of dopamine in the anaesthetized rat pretreated by phenoxybenzamine. If the depressor response to dopamine is mediated by PG, then inhibition of PG synthesis and release may attenuate or abolish the response of the vascular bed to the amine.

Seven male Sprague-Dawley rats (180–220 g) were anaesthetized with pentobarbitone (75 mg kg^{-1}, i.p.). A carotid artery was catheterized for the measurement of mean arterial pressure via a Statham P23 Db pressure transducer connected with an MA83 electromanometer. Another catheter was introduced into a jugular vein for drug administration. The rats were first given phenoxybenzamine (6 mg kg^{-1}, i.v.). Thereafter, the changes in mean arterial pressure induced by dopamine hydrochloride (25, 50, 100 μg^{-1}, i.v.) were studied before and re-evaluated 30 min after intravenous administration of indomethacin (5 mg kg^{-1}).

In another experiment, blood pressure responses to arachidonic acid (200 μg kg^{-1}, i.v.), PGE_1 (5 μg kg^{-1}, i.v.) and sodium nitroprusside (0·5 mg kg^{-1}, i.v.) given as a bolus, were measured in six anaesthetized rats pretreated with phenoxybenzamine, before and 30 min after indomethacin.

Dopamine hydrochloride produced a dose-dependent vasodepressor response in all rats; administration of indomethacin reduced the magnitude of this response (Table 1).

As expected, arachidonic acid, PGE_1 and sodium nitroprusside also produced hypotensive effects. Indomethacin did not affect the depressor action of sodium nitroprusside, rather it enhanced the hypotensive effect of PGE_1 and fully reduced the vasodepressor action induced by arachidonic acid (Table 2).

Table 1. *Changes in mean arterial pressure (MAP) elicited by dopamine (DA) before and 30 min after treatment by indomethacin in rats pretreated by phenoxybenzamine.* n = 7; values given are means with s.e.m.; Student's *t*-test was used to ascertain the results values + s.e.m.

	Before indomethacin (controls)	After indomethacin (5 mg kg^{-1}, i.v.)
Basal MAP (mm Hg)	97 ± 3·0	91 ± 4·1
Changes in MAP (mm Hg) DA (μg kg^{-1}, i.v.)		
25	—10·4 ± 1·2	—5·3 ± 0·8**
50	—19·8 ± 1·7	—11·2 ± 1·4***
100	—30·4 ± 2·7	—16·5 ± 1·9***

** $P<0·01$; *** $P<0·001$, difference from controls.

Table 2. *Effect of indomethacin on vasodepressor responses to arachidonic acid, PGE_1 and sodium nitroprusside in the rat.* n = 6; values given are means with s.e.m.; Student's *t*-test was used to ascertain the results values ± s.e.m.

	Before indomethacin (controls)	After indomethacin (5 mg kg^{-1}, i.v.)
Basal MAP (mm Hg)	87 ± 5	92 ± 3
Changes in MAP (mm Hg)		
Arachidonic acid (200 μg kg^{-1})	—39 ± 4·5	—14 ± 2·3***
PGE_1 (5 μg kg^{-1})	—23 ± 4·0	—36 ± 6·1*
Sodium nitroprusside (0·5 mg kg^{-1})	—24 ± 3·2	—26 ± 2·1

* $P<0·05$; *** $P<0·001$, different from controls.

* Correspondence.

Since the depressor effect of arachidonic acid was fully reduced 30 min after indomethacin, it is suggested that PG synthesis was effectively reduced in our experimental conditions. Nevertheless, it may also be assumed that indomethacin is not only a PG synthesis inhibitor, but also has unspecific properties, such as spasmolytic activity. In these conditions, indomethacin would have to attenuate responses to most agonists. Since the depressor response to dopamine, but not to PGE_1 or sodium nitroprusside, was reduced by indomethacin at a dose reducing PG synthesis but without effect on mean arterial pressure, data may thus suggest that, in the anaesthetized rat, the depressor response to dopamine may be partly due to the release of a dilator PG.

These observations are not in agreement with those of Dressler, Rossi & Orzechowski (1975) and Pendleton & Woodward (1976) who claimed that indomethacin did not antagonize the renal response to dopamine in dogs. On the one hand, differences in the species used may account for these discrepancies: it seems that the vascular bed of the rat might be different from that of the dog in the response to dopamine, since after treatment by α-adrenoceptor blocking agents the depressor effect of the amine was inhibited by haloperidol and morphine, respectively (van Rossum, 1966; Dhasmana, Dixit & others, 1969), in dogs, but not affected by these agents in rats (Aihara, Kasai & Sakai, 1972). On the other hand, it seems that, according to the nature of the vascular wall, dopamine may or may not be able to induce PG release, since indomethacin failed to attenuate the renal vasodilator action of dopamine in dogs (Dressler & others, 1975; Pendleton & Woodward, 1976), but reduced the coronary dilator response to the amine in the same animal (Takenada & Morishita, 1972).

Our data also support the role of PG in the systemic depressor response to dopamine in the anaesthetized rat.

December 27, 1977

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Bioavailability of phenytoin in lipid containing dosage forms in rats

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Phenytoin, a poorly water soluble drug, is erratically absorbed after oral administration in solid dosage form (Glazko & Chang, 1972; Lund, 1974). It has been reported that the bioavailability after oral administration of poorly water soluble drugs, particularly those that are lipophilic, can be improved by co-administration of lipid material (Greco, Moss & Foley, 1959; Crounse, 1961; Kraml, Dubue & Beall, 1962; Kabasakalian, Katz & others, 1970). There are no reports on the effect on the bioavailability of phenytoin when it is co-administered with vegetable oil or given in an emulsion form. Therefore, we have examined in rats the absorption profile of micronized phenytoin after its oral administration as an aqueous suspension, a corn oil suspension or a corn oil emulsion. The dosage forms of phenytoin (particle size 0·32 μm) were prepared in a suitable vehicle (Table 1). The corn oil emulsion was prepared by trituration and finally passing through a homogenizer; the suspensions were prepared by stirring with a mechanical stirrer. Each preparation was agitated at room temperature for 24 h before administration to ensure that the vehicles were saturated with phenytoin. The solubility of phenytoin in the different vehicles was measured by filtering through G-4 sintered glass filters and diluting the filtrate with 0·1 M NaOH; the absorbance was measured at 230 nm against a suitable blank.

Adult male albino rats, 300 to 340 g, were fasted for 20 h before and 12 h after drug administration. Phenytoin (20 mg kg^{-1}) in 0·5 to 1·2 ml of dosage form was placed in the stomach via a metal catheter, each dosage form was given to six rats. At 0·5; 1; 2; 3; 5; 7 and 12 h after administration, blood samples (0·3 ml) were collected from the tail vein. Serum was separated and frozen to −20° until radioimmunoassay (Cook, Kepler & Christensen, 1973). Serum concentrations were plotted against time and the area under the curve (AUC) was calculated by the trapezoidal rule. For

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