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Participation of prostaglandins in the vasodepressor effect of substance P

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With the availability of synthetic substance P of known structure and purity, the vasodepressor effect of the peptide has been extensively re-evaluated (Hallberg & Pernow 1975; Pernow & Rosell 1975; Burcher et al 1977; Bury & Mashford 1977; Eklund et al 1977; Losay et al 1977; Traczyk 1977). However, with few exceptions, the mechanism of the vasodepression or vasodilation induced by the peptide has not been identified. We have examined the dose-response (vasodepressor) profile of synthetic substance P in the anaesthetized dog and the effect thereon of several potential antagonists.

Fifteen mongrel dogs of either sex, 18 ± 1·0 kg were anaesthetized with sodium pentobarbitone (30 mg kg^{-1}, i.v.). The left femoral artery was cannulated for recording blood pressure via a Statham P-23 Dc pressure transducer and a Grass polygraph. Heart rate was continuously monitored via a Grass tachograph triggered by the arterial blood pressure pulse. The left femoral vein was cannulated for the infusion of supplemental doses of sodium pentobarbitone. The right femoral vein was cannulated with three PE-50 catheters. One was used to obtain a control dose-response curve to substance P (Peninsula Labs), and a second to obtain a dose-response curve to substance P after administration of the potential antagonist via the third catheter. The substance P doses ranged from 10^{-13} mol kg^{-1} (135 pg kg^{-1}) to 3×10^{-10} mol kg^{-1} (404 ng kg^{-1}). The doses of the potential substance P antagonists and the apparent efficacy of each in exerting its established action at the dose used were: 2 mg kg^{-1} atropine abolished acetylcholine (4 μg kg^{-1}, i.v.) depressor responses, 25 mg kg^{-1} pyribenzamine inhibited histamine (8 μg kg^{-1}, i.v.) depressor responses by 70% and 5 mg kg^{-1} propranolol inhibited isoprenaline (1 μg kg^{-1}, i.v.) depressor responses by 85 to 100% throughout the period that the second dose-response curve to substance P was generated. Preliminary experiments had established that a dose of 10 mg kg^{-1} of either indomethacin or meclofenamate (Parke Davis) abolished the depressor responses to arachidonic acid (1 mg kg^{-1}, i.v.) for longer than 5 h.

In another experiment, blood pressure responses to intravenously administered arachidonic acid (1 mg kg^{-1}), acetylcholine (4 μg kg^{-1}), histamine (8 μg kg^{-1}), isoprenaline (0·5 μg kg^{-1}), and prostaglandin E_2 (10 μg kg^{-1}) were measured before and 30 min after indomethacin (10 mg kg^{-1}, i.v.) in two anaesthetized dogs and after meclofenamate (10 mg kg^{-1}, i.v.) in another two dogs.

Substance P caused a dose-dependent vasodepressor response which was reproducible 60 min later in three dogs. The administration of indomethacin (3 dogs) or meclofenamate (3 dogs) altered the dose-response curves for substance P in an identical manner. In Fig. 1, it can be seen that inhibition of prostaglandin biosynthesis significantly reduced the magnitude of the vasodepressor response to substance P at 1 and 3×10^{-10} mol kg^{-1} as well as significantly shortened the duration of the vasodepressor responses elicited by the 3×10^{-11} to 3×10^{-10} mol kg^{-1} doses. This phenomenon was pronounced in a record of a preliminary experiment (Fig. 2). Blockade of acetylcholine (2 dogs), histamine (2 dogs), and β-adrenergic (2 dogs) receptors by atropine, pyribenzamine, and propranolol, respectively, had no discernible effect on the vasodepressor responses elicited by substance P over the dose range. Even though the tachycardia accompanying substance P administration was abolished by propranolol treatment, the vasodepressor responses were not significantly altered.

Neither indomethacin nor meclofenamate caused a significant attenuation of the vasodepressor responses to acetylcholine, histamine, isoprenaline or prostaglandin E_2, whereas the vasodepressor response to arachidonic acid was abolished. These results suggested that indomethacin and meclofenamate exerted a specific inhibitory effect on prostaglandin synthesis without evoking non-specific antagonist effects sometimes associated with the nonsteroidal inhibitors of prostaglandin synthesis (Flower 1974).

It is concluded that substance P-induced vaso-

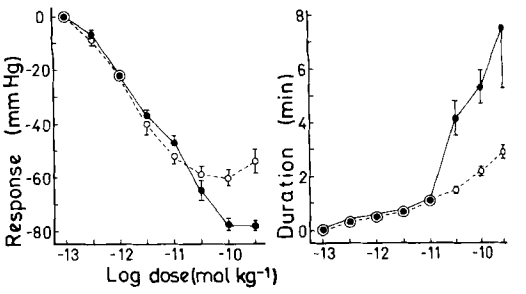

FIG. 1. Combined effects of indomethacin (3 dogs) and meclofenamate (3 dogs) at 10 mg kg^{-1} i.v. on the maximum changes in blood pressure and the duration of responses to various doses of intravenously administered substance P. ●—● Control. ○---○ PG biosynthesis inhibition.

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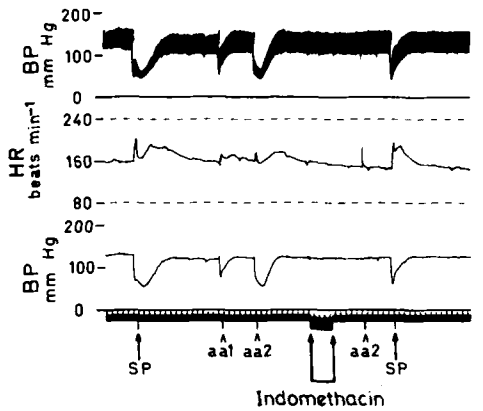

FIG. 2. The record of a preliminary experiment illustrating the effect of indomethacin at 10 mg kg^{-1} i.v. on the pulsatile blood pressure, heart rate, and mean blood pressure responses of an anaesthetized dog to intravenous substance P (SP) at 3 × 10^{-10} mol kg^{-1} (404 ng kg^{-1}) and arachidonic acid at 1 mg kg^{-1} (aa 1) and 2 mg kg^{-1} (aa 2). The time marks indicate 1 min intervals.

depressor responses, over the dose range studied, are not due partially or wholly to cholinergic, histaminergic, or β-adrenergic receptor stimulation. This confirms the conclusions reached by Pernow & Rosell (1975) from experiments on the mechanism of the effect of substance P on blood flow in canine adipose tissue and skeletal muscle. Eklund et al (1977) had observed that indomethacin did not alter the increase in human forearm blood flow during intravenous infusion of substance P. It was concluded that the vasodilation elicited by substance P was not mediated by the release of prostaglandins but rather was due to a direct effect of substance P on vascular smooth muscle. That this conclusion may not be relevant under all experimental conditions and in all species is evidenced by the results of the present study which clearly indicates that prostaglandins do participate in the vasodepressor responses to some doses of substance P in the anaesthetized dog.

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Potentiation of apomorphine-induced rotational behaviour by naloxone

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Previous research in our laboratories has established that pretreatment of animals with narcotic antagonist drugs produces significant enhancement of the effects of dopamine mimicking drugs. The hyperthermic effect of the dopamine mimicking drug apomorphine is increased by 50% if rabbits are pretreated systemically or centrally with naloxone (Quock 1977). Naloxone and naltrexone both significantly potentiate the anticataleptic activity of L-dopa in reserpinized mice (Namba et al 1980). This present communication reports our findings in still another experimental paradigm of central dopamine activity, apomorphine-induced rotational behaviour in rats with unilateral lesions of the nigrostriatal pathway.

Twelve male Sprague-Dawley rats (200–300 g, Gibco Animal Resources, Madison, Wisconsin) were anaesthetized with pentobarbitone and mounted in a stereotaxic headholder (David Kopf Instruments, Tujunga, California). A Radionics RFG-4 radiofrequency lesion generator was used to produce electrocoagulation lesions at stereotaxic coordinates localizing the substantia nigra (A 2·9, V −2·5, L ± 1·7) (Setler et al 1978). Beginning four days after surgery, animals were subjected to control apomorphine or naloxone/apomorphine experiments at four or five day intervals. The control experiments involved intraperitoneal injection of apomorphine 1·0 mg kg^{-1}, the animal was then placed into a rotometer for 30 min, during which rotations were recorded. The naloxone/apomorphine experiments involved intraperitoneal naloxone pretreatment at 1·0 mg kg^{-1} 5 min before the apomorphine challenge, followed by 30 min in the rotometer. Rats were tested with apomorphine or naloxone/apomorphine on an alternate basis for at least six total experiments (average: 7·8 ± 0·8 experiments per rat). Then they were killed for histological verification of the lesion sites.

Apomorphine hydrochloride (Merck) and naloxone

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