Table 1 The effect of i.v. prostaglandins E_1(PGE_1) and E_2(PGE_2) on the tachycardia induced by either sympathetic nerve stimulation or various drugs in the anaesthetized mouse

	Control response mean hr beats/min	*% Control Responses*					
		Dose PGE_1			*Dose PGE_2*		
		10 μg/kg	*20 μg/kg*	*40 μg/kg*	*10 μg/kg*	*20 μg/kg*	*40 μg/kg*
0.5 Hz	92 ± 7(30)	83 ± 2(4)	53 ± 9(5)	25 ± 7(3)	85 ± 5(7)	58 ± 10(7)	42 ± 5(4)
1 Hz	121 ± 5(29)	84 ± 3(4)	52 ± 6(5)	43 ± 4(3)	88 ± 2(6)	62 ± 2(5)	55 ± 8(6)
2 Hz	139 ± 7(29)	88 ± 2(5)	67 ± 5(6)	55 ± 5(4)	84 ± 8(5)	68 ± 7(5)	58 ± 14(4)
5 Hz	183 ± 7(25)	88 ± 5(5)	82 ± 7(4)	79 ± 10(4)	98 ± 1(4)	95 ± 2(4)	90 ± 2(5)
NA (1–2 μg/kg)	71 ± 5(19)	115 ± 8(4)	112 ± 9(3)	—	106 ± 9(4)	97 ± 4(6)	95 (2)
DMPP (100–300 μg/kg)	97 ± 10(9)	—	—	90 ± 11(3)	—	—	102 ± 8(6)
McN-A-343 (60–200 μg/kg)	93 ± 5(10)	—	—	11 ± 6(4)	—	—	22 ± 7(6)

Figures in parentheses indicate number of observations. All values are means ± s.e. mean. All doses of the stimulant drugs produced submaximal tachycardia.

Antagonism of noradrenaline's direct action on the effector organ is unlikely. Alternatively an effect on postganglionic neurones is possible because the prostaglandins can inhibit both responses to McN-A-343, which are mediated via muscarinic receptors on this structure (present paper), and noradrenaline release from electrically stimulated postganglionic nerves (e.g. Hedqvist & Wennmalm, 1971). However, an additional inhibition by prostaglandins of preganglionic acetylcholine release should be considered, since the prostaglandins failed to reduce the tachycardia caused by DMPP's stimulation of nicotinic receptors in the ganglia. This lack of an effect by the prostaglandins might be merely a function of dose or because DMPP-induced tachycardia relies heavily on amines released from the adrenals. Experiments are being conducted to investigate these possibilities.

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Interaction between the release of SRS-A and of prostaglandins

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Walker (1973) found in human chopped lung that treatment with indomethacin potentiated the release of SRS-A and suggested that prostaglandins inhibit its release. We investigated the effects of three non-steroid anti-inflammatory drugs on the release of SRS-A and histamine from sensitized guinea-pig lungs during challenge.

Lungs were removed from guinea-pigs previously sensitized to ovalbumen and rapidly perfused via the pulmonary artery with oxygenated Tyrode (37°C) at 5 ml/minute. Lungs were challenged by intra-arterial (i.a.) injection of ovalbumen (Sigma, grade III). The effluent was collected on ice for 10 minutes. The SRS-A content was estimated by immediately assaying aliquots of effluent on a strip of smooth muscle from guinea-pig ileum (blocked with mepyramine and hyoscine) against a laboratory standard preparation of

SRS-A. Results were expressed in arbitrary units. Histamine was assayed either biologically or fluorimetrically. Prostaglandin content was estimated by radioimmunoassay. Prostaglandin synthetase inhibitors were infused intra-arterially for 15 min before and during challenge.

Indomethacin (0.5–10 μg/ml) increased the amount of SRS-A released by up to 3.4 times (25 experiments). Treatment with indomethacin (1 μg/ml) produced the maximum increase in SRS-A (from 153 ± 26 to 525 ± 69 units/lung) and also reduced the output of prostaglandins. Histamine levels were also increased. Sodium aspirin (1–10 μg/ml) similarly potentiated release of SRS-A; the maximum increase produced by aspirin (5 μg/ml) was from 138 ± 26 to 465 ± 62 units/lung. This dose of aspirin also increased the amount of histamine released from 4.43 ± 0.6 to 19.5 ± 2.9 μg/lung as estimated by bioassay and fluorimetric assay (15 experiments).

Sodium meclofenamate 0.1–1.0 μg/ml increased SRS-A output by up to 2.4 times (maximum increase at 0.5 μg/ml i.a.; 16 experiments) and there was an increased amount of histamine released.

A bell-shaped dose-response curve was seen with all three drugs. The decreasing effects with increasing doses of anti-inflammatory drugs may be due to inhibition of enzymes such as phosphodiesterase.

Piper & Vane (1969) showed that a sample of SRS-A released rabbit aorta contracting substance (RCS; now thought to be a mixture of prostaglandin endoperoxides and thromboxane A_2 (Hamberg, Svensson & Samuelsson, 1975)) from unsensitized guinea-pig lungs. In the present experiments, injection of 0.5 units (laboratory standard) of two newly prepared samples of SRS-A i.a. into lung from unsensitized guinea-pigs released RCS and prostaglandins into the effluent (6 experiments).

These results suggest that SRS-A released in anaphylaxis may in turn release RCS and prostaglandins. They also strengthen the hypothesis that the prostaglandins then exert a negative feedback on further release of SRS-A. It is therefore not difficult to understand why inhibition of prostaglandin release by non-steroid anti-inflammatory drugs potentiates the release of SRS-A.

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Some properties of rabbit aorta contracting substance-releasing factor (RCS-RF)

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Rabbit aorta contracting substance-releasing factor (RCS-RF) was the name given by Piper & Vane (1969) to an unidentified factor distinct from slow reacting substance of anaphylaxis (SRS-A) found in the perfusate of immunologically shocked lungs from sensitized guinea-pig. RCS-RF injected into the pulmonary artery of perfused lungs from unsensitized guinea-pigs induced release of RCS, now thought to be a mixture of prostaglandin endoperoxides and their derivative, thromboxane A_2. We have now partially purified RCS-RF and describe some of its physiochemical and pharmacological properties.

Lungs from guinea-pigs sensitized to ovalbumin (Piper & Vane, 1969) were perfused with Krebs solution at 10 ml/min and shocked with ovalbumin (10 mg) injected into the pulmonary artery. Perfusate collected over the next 5 min was centrifuged at 5000 *g*, filtered, lyophilized and redissolved in distilled water to give about one tenth of the original volume. A batch of perfusate (about 50 ml) from a single lung contained 1000–2000 units of RCS-RF activity (defining 1 unit as that amount which gives the same release of RCS from perfused lung as 1 μg of arachidonic acid.)

The active principle was removed from the crude perfusate by adsorption onto Amberlite XAD-2 and was recovered from the resin in about 75% yield by elution, with ethanol-water (80:20, v/v), giving a preparation almost completely free of salts, proteins and histamine. The ethanol-water extract was dried *in vacuo* and washed three times with dry diethyl-ether.