injury³. The granulocytes, in turn, release more kinin from the available substrate and accelerate the inflammatory process. As the granulocytes accumulate and disintegrate, more kinins are destroyed than are formed and (as in our *in vitro* system) kinin levels fall. The character of a local inflammatory reaction would thus reflect complex interrelationships between kinins and granulocytes and undergo a gradual transition from the manifestations of kinin action to those of leucocyte accumulation.

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PHARMACOLOGY

Blockade by Propranolol of the Effect of Isoprenaline on Heart Rate and its Reversal by Methamphetamine

THE adrenergic receptors have been broadly classified into two groups: alpha and beta¹. Adrenergic receptors present in the mammalian cardiac muscle are now thought to belong to the beta type, and to initiate stimulation when occupied. Isoprenaline² is the catecholamine which best fits the beta receptor. The recently introduced drug propranolol hydrochloride (I.C.I. 45520; 'Inderal') is a

electrocardiograph. All solutions were made up in distilled water.

In eight dogs, isoprenaline sulphate 1 µg/kg, injected intravenously over a period of 10 sec (10 µg/ml. solution), produced a marked increase in heart rate (mean 32.29 ± S.D. 7.92 per cent). There was a marked fall in blood pressure (mean 52, range 42–68 mm of mercury). Both the heart rate and the blood pressure returned to normal in 5–7 min. After recording two control responses to isoprenaline in each animal, a 0.1 per cent solution of propranolol hydrochloride 0.3 mg/kg was injected intravenously. This drug produced a distinct decrease in the heart rate. The maximal effect was seen in about 5 min. 10 min after administration of propranolol, the injection of isoprenaline was repeated. There was no increase in heart rate in six experiments, while in two experiments the rate was increased by 6 and 12 beats/min. The heart rate did not return to control levels in either of these experiments (Table 1). The mean reduction in the effect of isoprenaline produced by propranolol was 96 per cent. The fall in blood pressure was completely blocked, and a brief pressor response was seen with isoprenaline (10–15 mm mercury). Another dose of isoprenaline also produced similar results. Methamphetamine 0.3 mg/kg, injected intravenously (0.1 per cent solution), produced a sustained rise in blood pressure (28–46 mm mercury). The heart rate increased gradually in five experiments, and in one of these experiments it reached the control level before propranolol was administered. In the remaining three experiments there was no increase in heart rate after methamphetamine. Injection of isoprenaline was then repeated. This drug now again increased the heart rate (mean 21.10 ± S.D. 5.26 per cent). This increase in rate was 34.54 per cent less than that produced in controls before propranolol injection. The results are summarized in Table 1. The blood pressure response was now biphasic; a brief pressor response (10–15 mm mercury) was followed by a brief depressor response (15–20 mm mercury). An increase in the dose of methamphetamine did not fully restore the effect of isoprenaline on heart rate. Similarly, a purely depressor response to isoprenaline could not be restored.

In the remaining four dogs, propranolol completely blocked the effect of isoprenaline on the heart rate. Repeated injections of adrenaline hydrochloride and noradrenaline bitartrate (5 µg/kg), ephedrine sulphate and methoxamine (0.3 mg/kg) failed to restore the isoprenaline response. The reversal of the blocking action of pro-

Table 1. EFFECT OF PROPRANOLOL AND METHAMPHETAMINE ON HEART RATE INCREASING EFFECT OF ISOPRENALINE

Experiment No.	Before propranolol			Heart rate after propranolol*			After methamphetamine†		
	Control heart rate	After isoprenaline‡	Increase in rate (%)	Control heart rate	After isoprenaline‡	Increase in rate (%)	Control heart rate	After isoprenaline‡	Increase in rate (%)
1	178	252	41.52	152	158	3.94	178	240	26.40
2	200	276	38.00	186	186	0.00	186	230	23.65
3	184	240	30.43	150	150	0.00	168	204	21.43
4	200	256	28.00	168	168	0.00	180	214	19.44
5	176	230	30.68	156	156	0.00	160	186	16.25
6	168	214	27.38	150	150	0.00	150	180	20.00
7	150	200	33.33	136	136	0.00	144	178	23.61
8	214	276	28.97	188	200	6.38	200	236	18.00

* Propranolol 0.3 mg/kg intravenously.

† Methamphetamine 0.3 mg/kg intravenously.

‡ Isoprenaline 1.0 µg/kg intravenously.

potent blocking agent for beta receptors, and it has been shown to block the action of isoprenaline in increasing the heart rate (J. Raventos, personal communication). In the present investigation, methamphetamine was found to antagonize this block, while adrenaline, noradrenaline, ephedrine and methoxamine were ineffective.

The experiments were performed in twelve mongrel dogs of either sex, weighing between 8 and 17 kg. The animals were anaesthetized with pentobarbitone sodium 35 mg/kg injected intravenously. Blood pressure was recorded from the right carotid artery with a mercury manometer. The right femoral vein was cannulated for injection of the drugs. The heart rate was recorded on an

pranolol by methamphetamine thus appears to be specific. The reversal was always incomplete. The mechanism of this reversal, and the effect of other pressor amines is being investigated.

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