tyramine given by other workers would not have interfered with the lipolytic action of the endogenous noradrenaline it released, because the lipolytic action of tyramine caused by it releasing noradrenaline is apparent at concentrations lower than those at which tyramine modifies its response to added noradrenaline.

This work was supported by Research Grant from U.S. Public Health Service (HE 11848).

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Effect of capsaicin on the guinea-pig isolated atrium

Capsaicin (decanoic acid vanillylamide), the pungent principle present in various species of capsicum, is recognized as one of the most active substances in causing excitation of sensory nerve endings. In the cat or dog, circulatory and respiratory effects like hypotension, bradycardia and apnoea are especially pronounced. Since these symptoms occur when capsaicin is injected intravenously but are abolished by vagotomy, the mechanism of these effects is generally believed to be the result of stimulation of the chemo- or stretch receptors in the lung or coronary regions. Additional experiments are needed to fully elucidate this mechanism (Pórszász, György & Pórszász-Gibiszer, 1955; Coleridge, Coleridge & Luck, 1965; Mitchell, Dwarka & Stephen, 1967; Molnár & György, 1967; Molnár, Makara & György, 1967).

In studying the effects of thiamine derivatives on the guinea-pig atrium, Fujiwara & Fukuda (1969) discovered that the extract of *Capsicum annuum* caused a marked increase in the heart rate and enhanced the contraction of the atrium in a manner similar to adrenaline and that this action is due to capsaicin, an ingredient of *Capsicum annuum*.

Guinea-pigs, either male or female, 250 to 300 g were bled out by cutting the common carotid arteries without severing the vagi. The heart was quickly removed and immersed in oxygen saturated Locke-Ringer solution of the following composition (mM): NaCl 154, KCl 56, $CaCl_2$ 2·2, $NaHCO_3$ 2·4, and glucose 5·6 in 1 litre of distilled water. After the extraneous tissues were removed the atrium was suspended in a 50 ml bath containing Locke-Ringer solution aerated with oxygen at 30° and spontaneous contractions of the atrium recorded with an isotonic lever. After the beat of the atrium reached equilibrium, each drug was administrated into the bath. Pure crystalline capsaicin (Kusuge, Inagaki & Uehara, 1958) from the fresh fruits of *C. annuum* var *parvo-acuiminatum* Makino, was used in the experiment. As capsaicin was not readily soluble in water, the reagent was prepared as follows: capsaicin

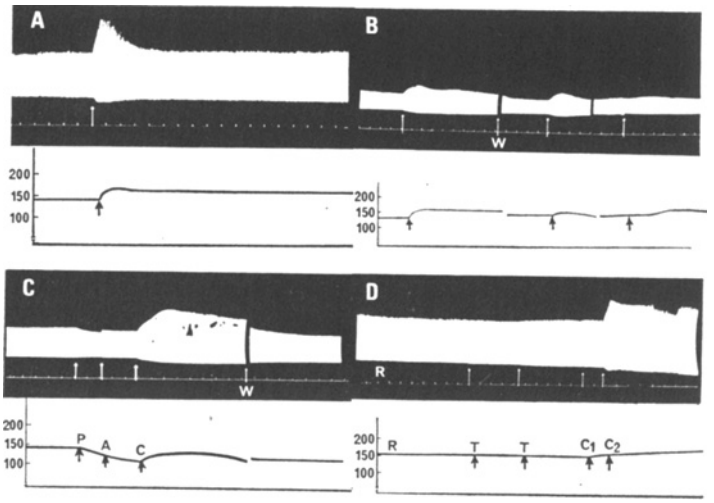

FIG. 1. Responses of atrium (upper traces) and heart rate/min (lower traces) to capsaicin. A. Addition of capsaicin (0·5 μg) to bath at arrow. B. Repeat of inotropic effect of capsaicin (0·5 μg at arrows) after the atrium was washed with Ringer-Locke solution. C. Response of atrium to capsaicin (C↑ 0·5 μg) made unresponsive to adrenaline (A↑ 10 μg) by pretreatment with propranolol (P↑ $7{\cdot}7 \times 10^{-8}$ M). D. Response of atrium to capsaicin (C_1 0·1, C_2 0·4 μg ↑) after it had been made unresponsive to tyramine (T↑ 100 μg) by pretreatment with reserpine (5 mg/kg) 24 h previously.

(1 mg) was dissolved in ethanol (5 ml) and then diluted to 100 ml with distilled water. Tests were made on both the synthetic capsaicin and capsaicin II (the pungent principle present in capsicum; its chemical structure differs from capsaicin at the point of saturation of the double bond of decylenic acid only (Kusuge, Inagaki & Niwa, 1958).

The addition of capsaicin to the bath caused a sudden and marked increase in the amplitude of the atrium contraction, an effect demonstrable at concentrations as low as $1{\cdot}6 \times 10^{-9}$ M (Fig. 1A). This inotropic effect was repeated when capsaicin was added again after the atrium was washed with Locke-Ringer solution as shown in Fig. 1B.

Fig. 1C shows the results when capsaicin was added to the atrium which had been made unresponsive to adrenaline by pretreatment with $7{\cdot}7 \times 10^{-8}$ M propranolol. A marked effect of capsaicin on atrial contraction can still be seen under these conditions. Capsaicin also exhibited the same inotropic effect when the atrium had been made unresponsive to tyramine (Fig. 1D) by pretreatment with reserpine (5 mg/kg weight) which was injected intraperitoneally 24 h beforehand.

From these observations there seems little doubt that the capsaicin effect is different from and independent of adrenaline.

The authors express gratitude for synthetic capsaicin to Professor Mitsuo Takahashi in the Toohoku Pharmacological College.

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Relative blocking effectiveness of propranolol and of practalol [4-(2-hydroxy-3-isopropylaminopropoxy) acetanilide] on isoprenaline in β-1 receptor mediated calorigenesis*

Barrett, Crowther & others (1968) have shown practalol [ICI 50172; 4-(2-hydroxy-3-isopropylaminopropoxy) acetanilide] to be about one third as effective as propranolol in blocking isoprenaline in previously defined (Arnold, McAuliff & others, 1966; Lands, Arnold & others, 1967) β-1 receptor mediated lipolytic or cardiac effects. However, practalol was only about 1/100 as effective as propranolol in antagonizing reference catecholamines in previously defined (Arnold & others, 1966; Lands & others, 1967) β-2 receptor mediated bronchodilatation or vasodepression. Since we have shown (Arnold & McAuliff, 1968) that calorigenesis (non-shivering thermogenesis) in the rat, based on oxygen uptake, is β-1 receptor mediated, we were prompted to compare the blocking effectiveness of propranolol and of practalol on isoprenaline under these *in vivo* conditions.

The method we used was modified slightly from that of MacLagan & Sheahan (1950) for mice. Briefly, groups of three, 60 to 90 g, *ad libitum* fed, conscious rats were placed in a small but adequate sized wire basket which was placed, in turn, in a 10-inch dessicator at 28°. The dessicator previously had been flushed with oxygen for a few minutes. The oxygen uptake of the rats was monitored by an appropriately inter-connected Med Science Electronics (St. Louis) Model 160 Spirometer. The comparisons are based on the oxygen taken up over the 10- to 25-min period after administering a test compound, a 10 min equilibration having been judged to be adequate.

Table 1. *Comparison of blockade of (—)-isoprenaline in calorigenesis in the rat by propranolol or by practalol. Three rats per trial*

Isoprenaline* (μg/kg)	Blocking agent† (mg/kg)	No. of trials	O_2 Uptake Mean ± s.e. (cc/100 g/min)	O_2 Uptake % Control
None	None	6	3·57 ± 0·13	
Isoprenaline, 4	None	5	4·45 ± 0·25	125
Isoprenaline, 12	None	6	6·21 ± 0·53	170
None	None	4	3·19 ± 0·12	
Isoprenaline, 12	Propranolol, 3·16	4	4·39 ± 0·53	140
Isoprenaline, 12	Propranolol, 10·0	4	3·46 ± 0·17	110
None	None	8	2·91 ● 0·18	
Isoprenaline, 12	Practalol, 31·6	4	4·20 ± 0·12	140
Isoprenaline, 12	Practalol, 100	3	3·19 ± 0·10	110

* Test agents as base. Compounds used as the hydrochlorides. Test agents given s.c.
† Blocking agent given ½ h before isoprenaline.

* Presented, in part, at the Fall Pharmacology Meetings, Pittsburgh, August 24–28, 1969.