A screening method for antiarrhythmic agents in the rat

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A method using rats for determining the potential of new compounds as antiarrhythmic agents has been developed. It is based on the antagonism displayed by antiarrhythmic drugs to the ventricular fibrillation that occurs after respiratory arrest induced by chloroform. Similar effects have been observed in mice (Lawson, 1968).

The compounds to be tested are given by intraperitoneal injection to groups of ten rats of either sex and weighing 90 to 100 g. Each group receives a different dose level and the controls receive the vehicle. One hour later each rat is placed in the anaesthetic chamber and anaesthetized with chloroform. Immediately after respiratory arrest electrodes are attached to the animal and the electrocardiogram (Standard lead II) is monitored. If fibrillation occurs during the monitoring period then the time of onset after respiratory arrest is noted. If no fibrillation occurs then the animal is regarded as being protected.

No ventricular fibrillation was observed in animals killed by ether inhalation or cervical dislocation. Therefore the cardiac arrhythmias are probably due to the effects of chloroform on the heart. The three antiarrhythmic agents quinidine, lignocaine and procainamide displayed a clear antagonistic activity to the chloroform induced arrhythmias, their ED50s being respectively 11·5, 17·4 and 20·9 mg/kg.

The effects of drugs that interfere with sympathetic nerve function were also investigated as sympathetic hyperactivity has been implicated in the production of cardiac arrhythmias during chloroform anaesthesia. The adrenergic neurone blocking agents bretylium and guanethidine (1 to 5 mg/kg) were more active in the test than quinidine, and the response to bretylium (5 mg/kg) was antagonized by the concomitant administration of dexamphetamine (3 mg/kg). Inconsistent results were obtained with the ganglion blocking agents hexamethonium and pentacynium. Doses lower than 5 mg/kg exhibited a variable protective action and higher doses did not protect more than 60% of the animals in each group.

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The effect of cyproheptadine on food consumption in the fasted rat

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Cyproheptadine is reported to stimulate appetite and to increase body weight in man (Bergen, 1964; Gionta, 1969; Noble, 1969) and in cats (Chakrabarty, Pillai, Anand & Singh, 1967), but not in mature dogs nor mature or weanling rats or guinea-pigs (Bergen, 1964). However, we find increased food consumption in fasted rats.

The rats were pre-trained to an overnight fasting schedule and kept on wire grid floors. Food was removed daily at 16.30 and was replaced the following morning for a 6 h period, 30 min after administering cyproheptadine hydrochloride sub-

cutaneously in 0·25% Celacol suspension. The procedure was repeated on each of four successive days.

(i) *Studies using food hoppers with grouped rats* ($n=4$). In each of five experiments with rats of either sex (mean body weight range 114–200 g) food and water consumption and body weight were recorded every 2 h. Food consumption in the cyproheptadine treated groups (6·2–50 mg/kg) was consistently higher than in controls during the first 2 h but the total daily food consumption only exceeded control values on days 3 and 4.

(ii) *Continuous recording of food consumption in individually housed rats.* A mechanical device (to be published) was used for recordings from six female rats in two experimental sessions spaced a fortnight apart when their mean body weights were 122 g and 206 g respectively. Discrete meals were recorded. Commencing almost immediately following food presentation, control animals ate their first meal over a period of about 1 h and they usually had a further two, and occasionally three or four meals.

TABLE 1. *Effect of cyproheptadine on the consumption of meals by fasted rats*

	Meal 1			Meal 2	
Treatment	Amount (g)	Duration (min)	Mean eating rate (g/min)	Amount (g)	Duration (min)
Controls (0·25% Celacol s.c.)	7·0	62	0·11	3·5	38
Cyprohetadine 12·5 mg/kg s.c.	9·8*	125*	0·08	4·2	63
Cyproheptadine 25 mg/kg s.c.	9·4	118*	0·08	2·8	44

Means for four rats on days 1–4. * Different from control value at 1% level of significance.

Cyproheptadine (12·5 and 25 mg/kg) significantly prolonged the duration of the first meal and the lower dose significantly increased food consumption (Table 1). Eating rate and the number of meals taken were decreased: on only a few occasions were more than two meals eaten. The appetite stimulant effect persisted for the same duration (2 h) as the increased electrical activity observed with the same drug in the " feeding centre " in the lateral hypothalamus of cats (Chakrabarty *et al.*, 1967).

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Initial suppression of the locomotor stimulant response to dexamphetamine in rats exposed to a novel environment

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The effect of dexamphetamine on the activity in rats is dependent upon their previous experience: in Y-maze studies, amphetamine either increased (Rushton & Steinberg, 1963) or had little effect (Marriott, 1968) upon the activity of " inexperi-