Br. J. Pharmac. (1974), 52, 605-608

SUPERSENSITIVITY TO ISOPRENALINE INDUCED IN RATS BY PROLONGED ISOLATION

ZIPORA SPEISER & MARTA WEINSTOCK

Department of Physiology and Pharmacology, Sackler School of Medicine, Tel Aviv University, Ramat Aviv, Israel

1 The effect of isoprenaline on diastolic blood pressure and heart rate was determined in anaesthetized male rats which had been housed individually for 6-8 weeks after weaning, and compared with its effect in group-housed litter-mate controls.

2 Isoprenaline caused a significantly greater fall in diastolic pressure in isolated rats and a greater increase in heart rate.

3 Low doses of noradrenaline (5-10 ng) caused vasodepressor responses in isolated, but not in group-housed rats.

4 The pressor response to noradrenaline, which was smaller in isolated rats, was increased to the level of group-housed controls by (±)-propranolol.

5 Prolonged isolation of rats may bring about an increase in sensitivity of β-adrenoceptors to isoprenaline and noradrenaline.

Introduction

Prolonged isolation of mice or rats has been found to result in behavioural abnormalities, including irritability, aggressiveness and hyperactivity (Valzelli, 1973). We have recently reported that propranolol can reduce the hyperactivity of isolated rats to that found in group-housed controls, without affecting activity of normal rats (Weinstock & Speiser, 1973).

Welch & Welch (1965; 1968) found that isolation of mice resulted in a reduced turnover of noradrenaline in both the brain and adrenal gland. To explain the behavioural abnormalities of isolated mice, they suggested that a reduced release of noradrenaline that occurs during the isolation period may cause a relative supersensitivity of catecholamine receptors. When placed in a novel situation or with other mice, even a normal release of noradrenaline in singly-housed animals could produce an exaggerated response.

The purpose of the present study was to see whether prolonged isolation causes any change in the response of peripheral α- or β-adrenoceptors to catecholamines.

Methods

Male Wistar albino rats were housed in individual cages or in groups of 4 immediately after weaning as described by Weinstock & Speiser (1973). Six to eight weeks later, when the animals weighed 250-280 g, a solitary-housed and a group-housed rat were anaesthetized simultaneously with sodium pentobarbitone (60 mg/kg subcutaneously). Both animals were prepared for recording of blood pressure by means of a cannula in the left carotid artery, attached by a Statham pressure transducer P23AC to a multichannel polygraph. Drugs were injected in a volume of 0.1 ml through a cannula in the right femoral vein.

Dose-response curves for the lowering of diastolic pressure induced by isoprenaline were established in 9 pairs of such rats. Any pair of rats in which there was an initial difference in diastolic pressure of more than 15 mmHg was discarded. The effect of several doses of isoprenaline on heart rate was also studied in isolated and control rats.

In a further 8 pairs of rats, dose-response curves were established for the rise in systolic pressure caused by noradrenaline. In some rats the effect of noradrenaline was studied before and after administration of (±)-propranolol.

The following drugs were used: isoprenaline sulphate, noradrenaline bitartrate, (±)-propranolol hydrochloride (Abic Ltd.), and pentobarbitone sodium (Nembutal). Doses are expressed in ng of the salt injected per rat.

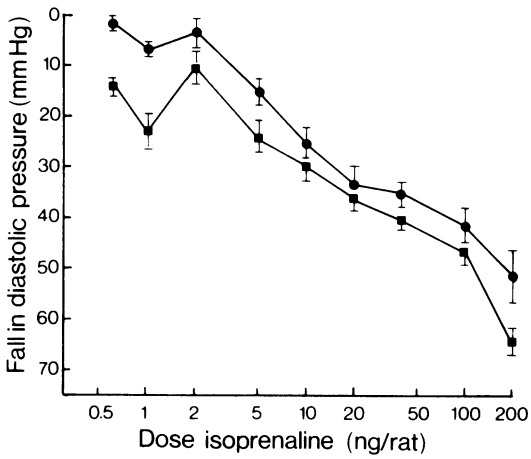

Fig. 1 Effect of isoprenaline on diastolic pressure of (•) group-housed and (▪) isolated rats.

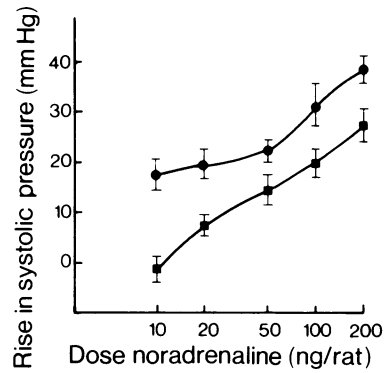

Fig. 2 Effect of noradrenaline on systolic pressure of (•) group-housed and (▪) isolated rats.

Results

Isolation of rats for 6-8 weeks did not cause any significant change in the basic systolic or diastolic pressures after pentobarbitone anaesthesia. The systolic/diastolic pressure for group-housed rats was 134.4 ± 32/117.6 ± 27 mmHg, and 128.8 ± 18/112 ± 13 mmHg for solitary-housed rats. There was no difference in the basic heart rate of the two groups of rats, the mean values being 362 ± 43 beats/min for controls and 346 ± 26 beats/min for isolated rats.

Isoprenaline consistently produced a greater lowering of diastolic pressure in the individually-housed rat than in the group-housed animal tested at the same time. The duration of response to isoprenaline was also prolonged in isolated rats. This enhanced responsiveness to isoprenaline was particularly marked at lower doses (0.5to 2 ng) and was significant at 5% P level at 0.5, 1, 5, 100 and 200 ng doses (See Figure 1).

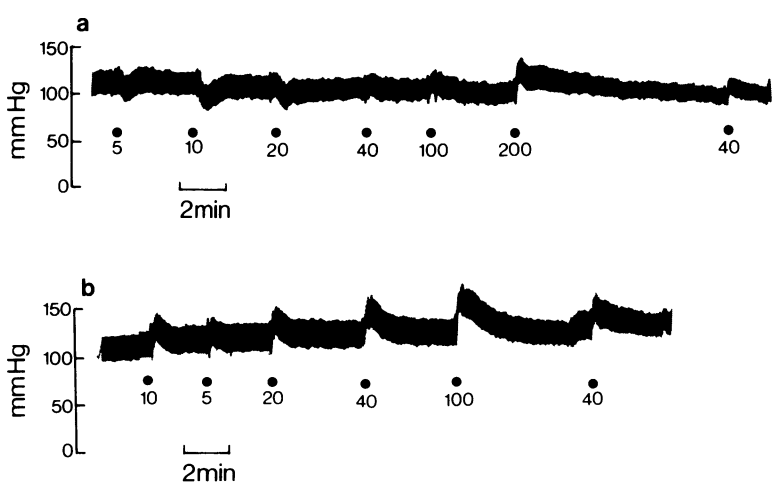

Fig. 3 The effect of noradrenaline on the blood pressure of an isolated and group-housed rat. (a) Blood pressure responses isolated ♂ rat (280 g) anaesthetized with sodium pentobarbitone (60 mg/kg) to intravenous injections of noradrenaline. Doses expressed in ng per rat. (b) Blood pressure responses of group-housed ♂ rat (278 g) anaesthetized with sodium pentobarbitone (60 mg/kg) to intravenous injections of the same doses of noradrenaline as above. Note that low doses of noradrenaline caused a depressor response in the isolated rat but not in the group-housed rat.

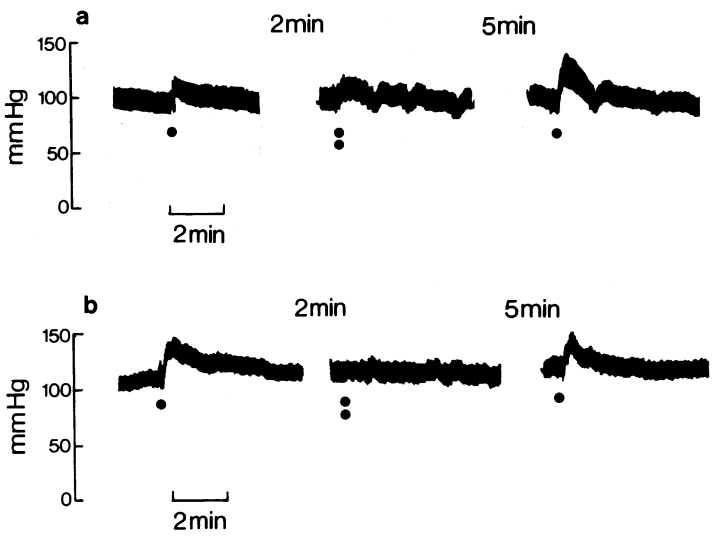

Fig. 4 The effect of (±)-propranolol on the pressor responses to noradrenaline: (a) from isolated ♂ rat (258 g) and (b) from group-housed control ♂ rat (262 g). Both rats were injected intravenously with noradrenaline (100 ng) at single dot, and (±)-propranolol (50 μg) at double dots.

Table 1 Effect of isoprenaline on the heart of isolated and group-housed rats

Dose isoprenaline (ng/rat)	*Group-housed rat Mean inc. heart rate ± s.e. (beats/min)*	*No. of rats*	*Isolated rats Mean inc. heart rate ± s.e. (beats/min)*	*No. of rats*
1	0	4	6.3 ± 4.5	4
2	2.5 ± 3.7	5	8.0 ± 5.0	5
4	*2.5 ± 3.2	6	*25 ± 9.5	6
15	31.4 ± 9.0	8	32 ± 8.3	8
40	30 ± 11	4	31 ± 12.0	4

* Difference significant at 1% level.

In contrast, the rise in systolic pressure produced by noradrenaline was significantly less in isolated than in group-housed rats (Figure 2). In 4 isolated rats noradrenaline (5-10 ng) caused a fall in both systolic and diastolic pressure of 5-15 mmHg, when it was injected before any larger amount had been given. After 50 or 100 ng, the original small amounts (5-10 ng) caused either a much reduced or no vasodepressor response. Such a hypotensive effect was not seen when small doses of noradrenaline were injected to control rats (Figure 3).

Injection of (±)-propranolol, 50 μg, caused a transient rise in blood pressure of 5-10 mm in 2 out of 3 isolated rats but not in 3 group-housed animals. When the blood pressure had returned to its control level after propanolol, the pressor response to 100 ng noradrenaline was increased to control levels in isolated rats, from 15 to 25-30 mmHg. Higher levels of propranolol (0.1-0.5 mg) caused no further increase in isolated rats and did not modify the pressor response to noradrenaline in control animals (Figure 4).

The effect of isoprenaline on heart rate was very variable, particularly at the lower dose range in isolated rats. Nevertheless it was possible to demonstrate a significantly greater positive chronotropic effect of isoprenaline in the isolated rat at a dose of 4 ng (See Table 1).

Discussion

When rats were isolated for 6-8 weeks the cardiovascular system became more responsive to isoprenaline. At low doses (0.5-5 ng) isoprenaline

caused a 5 to 10-fold greater fall in diastolic pressure in such animals than in group-housed litter-mate controls. At higher doses (10-200 ng) the difference in response to isoprenaline was less between the two groups, being only 2-fold.

At a dose of 4 ng, isoprenaline also caused a significantly greater increase in heart rate in the solitary-housed rats. At lower doses the response was too variable to permit a demonstration of significantly raised sensitivity.

The pressor effect of noradrenaline, on the other hand, was less in the isolated than in the control rats. This diminished responsiveness to noradrenaline does not appear to have resulted from reduced ability of the vessels to constrict, since the full effect was restored after β-adrenoceptor blockade by propranolol. Rather it appears to be due to an increase in the vasodilator effect of noradrenaline, an effect that could be demonstrated only in isolated rats in doses below 10 ng.

Since propranolol treatment did not increase the pressor response to noradrenaline in the isolated rat above that obtained in the group-housed animal, it suggests that isolation increases only the sensitivity of β-receptors to catecholamines, while that of α-receptors remains unchanged.

This work forms part of a Ph.D. thesis to be submitted to Tel Aviv University.

References

VALZELLI, L. (1973). The isolation syndrome in mice. *Psychopharmacolgia,* **31**, 305-320.

WEINSTOCK, M. & SPEISER, Z. (1973). The effect of *dl*-propranolol, *d*-propranolol, and practolol on the hyperactivity induced in rats by prolonged isolation. *Psychopharmacologia,* **30**, 241-250.

WELCH, B.L. & WELCH, A.S. (1965). Effects of grouping on the level of brain norepinephrine in white Swiss mice. *Life Sci.,* **4**, 1011-1018.

WELCH, B.L. & WELCH, A.S. (1968). Greater lowering of brain catecholamines in group-housed than in individually-housed mice administered D.L.-methyl tyrosine. *J. Pharm. Pharmac.,* **20**, 244-248.

(Received April 3, 1974)