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COMPARISON OF THE ANTI-HYPERTENSIVE RESPONSE TO β-ADRENOCEPTOR BLOCKING DRUGS IN INTACT AND ADRENAL-DEMEDULLATED SPONTANEOUSLY HYPERTENSIVE RATS

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1 The β-adrenoceptor blocking drugs atenolol, metoprolol, practolol, propranolol, timolol and oxprenolol (as racemates) were administered acutely at three dose levels (0.01, 0.03 and 0.1 mmol/kg i.p. or s.c.) to spontaneously hypertensive rats with intact adrenal glands (SH-rats) and following unilateral adrenalectomy and contralateral adrenal-demedullation (SHAD-rats). Changes in mean arterial pressure and heart rate were determined via an indwelling aortic catheter, with the animals placed in a quiet environment.

2 All drugs significantly lowered the blood pressure of SHAD-rats, and these responses were not always associated with changes in basal heart rate.

3 With the exception of metoprolol and atenolol, the β-adrenoceptor blocking drugs were less effective as anti-hypertensives in SH- than in SHAD-rats. Notably, timolol and oxprenolol lowered the blood pressure of SH-rats at low doses only, whereas propranolol evoked a pressor response in this model.

4 Whilst (+)-propranolol lowered the blood pressure of SHAD-rats only at a dose which caused myocardial depression, the anti-hypertensive response to (−)-propranolol did not parallel changes in heart rate and was preceded by a pressor response.

5 The results imply that adrenal catecholamine release contributes towards masking the anti-hypertensive effects of some β-adrenoceptor antagonists in SH-rats.

Introduction

Progress in identifying the mechanism(s) involved in mediating the anti-hypertensive activity exhibited by β-adrenoceptor blocking drugs in man, has been impeded by the absence of a suitable animal model for laboratory studies. Although the spontaneously hypertensive (SH) rat has been used extensively to study the aetiology of hypertensive disease and to investigate the mechanisms responsible for mediating the effects of clinically useful anti-hypertensive drugs, it, like other laboratory animal preparations, has proved to be of limited value in studying the anti-hypertensive properties of β-adrenoceptor blocking drugs (see review by Buckingham & Hamilton, 1979). It is feasible that the ability of these drugs to stimulate adrenal catecholamine release (Nakano & Kusakari, 1965; 1966; Kayaalp & Kiran, 1966; Kayaalp & Türker, 1967; Dasgupta, 1968; Yamamoto & Sekiya, 1969; Regoli, 1970; Eliash & Weinstock, 1972; Regoli, Regoli & Gysling, 1972; Nakao, Kato & Takagi, 1975) could be responsible for masking their blood pressure lowering activity in conscious animals. In this respect, unilateral adrenalectomy and contralateral adrenal demedullation has been shown to unmask a blood pressure lowering effect of oxprenolol in one-kidney renal hypertensive rats (Brunner & Hedwall, 1970), and to augment the anti-hypertensive response to pindolol in deoxycorticosterone acetate (DOCA)/saline-treated rats (Buckingham, Hamilton & Robson, 1978). The present study was designed to examine the possibility that surgical ablation of the adrenal medullae might unmask an anti-hypertensive effect of β-adrenoceptor blocking drugs in SH-rats.

Methods

Female SH-rats of the Japanese strain (Okamoto & Aoki, 1963) were used throughout.

Surgical ablation of the adrenal medullae and implantation of a catheter for direct measurement of arterial blood pressure

At age 10 to 12 weeks, some SH-rats were anaesthetized with methohexitone sodium, 45 mg/kg intraperitoneally (i.p.), and subjected to unilateral adrenalec-

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tomy and contralateral adrenal-demedullation (SHAD-rats). At age 17 to 22 weeks, a polyethylene catheter was implanted in the abdominal aorta of both SH- and SHAD-rats, using a method described previously (Buckingham, 1976). The rats were housed in single cages in a quiet room and allowed 18 to 24 h to recover before use.

The fact that all animals were exposed to surgical trauma only shortly before experiments were undertaken is, in our opinion, sufficient justification for not performing a bilateral laparotomy (Sham-operation) in control animals at the time of surgical adrenal ablation in their SHAD-rat counterparts.

Direct measurement of arterial pressure and heart rate in conscious rats

Mean arterial pressure was recorded in conscious, unrestrained animals with a Bell & Howell pressure transducer (1 mmHg ≈ 133 Pa) connected to a Devices recorder; heart rate was obtained from a rate-meter triggered by the arterial pulse wave. Measurements of mean arterial pressure and heart rate were made immediately before dosing (zero time) and then at hourly intervals for the next 4 or 5 h.

Drug administration to conscious rats

Drugs were dissolved or suspended in 0.9% w/v NaCl solution (saline) and injected subcutaneously (s.c.) or i.p. at doses of 0.01, 0.03 and 0.1 mmol/kg. Control rats in each experiment received vehicle only (2 ml/kg). Each experiment was performed on 2 or 3 separate occasions, with different batches of rats, and the results ultimately pooled to provide group sizes of 10 to 15 rats. In preliminary studies, oxprenolol and practolol, administered s.c. to SHAD-rats, were only marginally anti-hypertensive. Blood pressure lowering activity of both drugs was greatly improved following i.p. injection and this route was adopted for the purpose of comparing their effects in SH- and SHAD-rats. Other test compounds were administered s.c. in both models.

Drugs

The effects of the following drugs were studied: atenolol, practolol, (±), (−) and (+)-propranolol hydrochloride (ICI); metroprolol tartrate (Geigy); oxprenolol hydrochloride (Ciba); timolol maleate (Merck, Sharp & Dohme).

Statistical analysis

All blood pressure and heart rate changes were related to the values at zero time and the significance of differences between control and treated groups evaluated by Student's t test. Values of $P < 0.05$ were considered to be significant.

Results

Effect of β-adrenoceptor blocking drugs on the blood pressure and heart rate of SH- and SHAD-rats

Atenolol Each dose of atenolol (0.01, 0.03 and 0.1 mmol/kg s.c.) caused a fall in blood pressure similar in magnitude and time-course; the maximum anti-hypertensive response developed over 3 to 4 h after dosing in both SH- and SHAD-rats (Figure 1a and b). The bradycardia was also unrelated to dose but, by contrast, developed rapidly (1 h after injection) and persisted for the duration of the experiment in both models (Figure 1c and d).

Metoprolol Metoprolol also significantly lowered the blood pressure and heart rate of both SH- and SHAD-rats at all dose levels (0.01, 0.03 and 0.1 mmol/kg s.c.) (Figure 2). These effects of metoprolol were dose-dependent to the extent that in both models the highest dose caused significantly greater reductions in blood pressure (Figure 2a and b) and heart rate (Figure 2c and d) than the lowest dose at 4 h. Whereas the changes in blood pressure evoked by metoprolol developed over 3 h, the maximum heart rate response was observed at 1 h; thereafter the bradycardia progressively diminished.

Practolol Practolol (0.01, 0.03 and 0.1 mmol/kg i.p.) proved to be more effective as an anti-hypertensive in SHAD- than in SH-rats (Figure 3a and b). In the former rats, the anti-hypertensive response to practolol occurred more rapidly (1 to 2 h) than with atenolol or metoprolol. Heart rate was little changed by practolol in either model. However, the tendency of control group mean heart rates to increase during the course of each experiment resulted in small, but statistically significant, net reductions in heart rate following practolol 0.01 (2 h) and 0.1 (1 h) mmol/kg in SH-rats, and following 0.01 (4 h), 0.03 (2, 4 h) and 0.1 (2, 4 h) mmol/kg in SHAD-rats (Figure 3c and d).

Timolol In SH-rats, only the lowest dose of timolol (0.01 mmol/kg s.c.) proved to be anti-hypertensive (3 to 4 h) (Figure 4a). However, in SHAD-rats, each dose of timolol (0.01, 0.03 and 0.1 mmol/kg s.c.) caused a similar, significant reduction in blood pressure 2 to 4 h after drug administration. In both models, timolol produced bradycardia which was independent of dose, rapid in onset (1 h) and sustained for the duration of the experiment (Figure 4c and d).

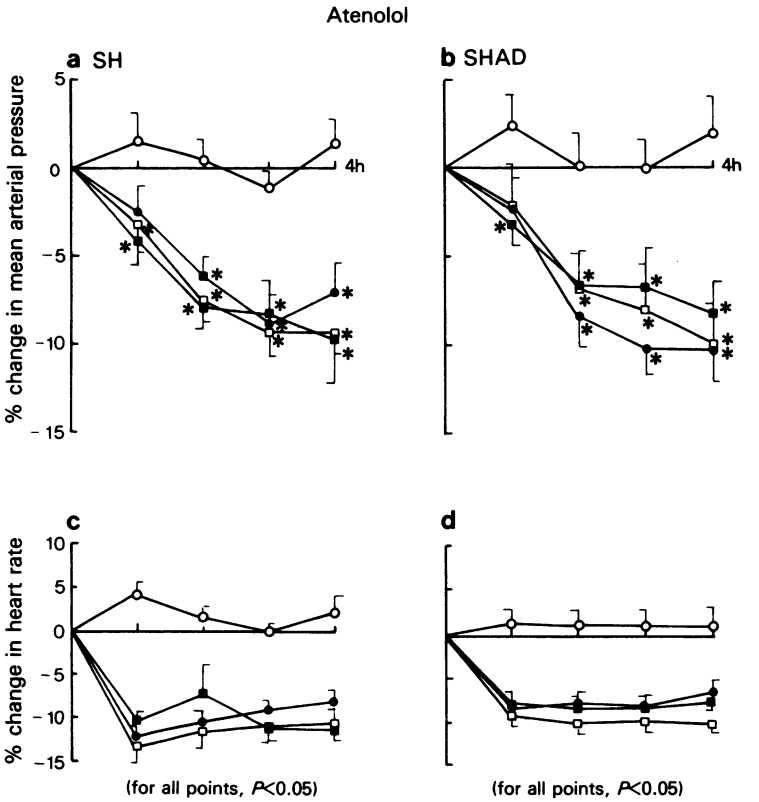

Figure 1 Effect of atenolol on mean arterial pressure and heart rate in SH- and SHAD-rats; 0.01 mmol/kg (●), 0.03 mmol/kg (□), 0.1 mmol/kg (■) s.c. or control vehicle (○). Vertical bars show s.e. mean; $n = 15$ rats; * show significant ($P < 0.05$) differences between treated groups and control group. In SH-rats the basal mean blood pressure and heart rate of each group were, respectively, for atenolol 0.01 mmol/kg, 140 ± 4 mmHg and 343 ± 11 beats/min; for 0.03 mmol/kg, 139 ± 5 mmHg and 346 ± 11 beats/min; for 0.1 mmol/kg, 140 ± 4 mmHg and 333 ± 8 beats/min; and for the control group, 140 ± 3 mmHg and 336 ± 6 beats/min. In SHAD-rats the corresponding figures were as follows: for atenolol 0.01 mmol/kg, 144 ± 2 mmHg and 320 ± 6 beats/min; for 0.03 mmol/kg, 143 ± 3 mmHg and 327 ± 7 beats/min; for 0.1 mmol/kg, 144 ± 2 mmHg and 315 ± 6 beats/min; and for the control group 142 ± 2 mmHg and 325 ± 7 beats/min.

Oxprenolol As with practolol and timolol, oxprenolol proved to be more effective as an anti-hypertensive in SHAD- than in SH-rats. Thus, in SH-rats, the only significant reduction in blood pressure was seen at 2 h after 0.01 or 0.03 mmol/kg i.p. (Figure 5a). By contrast, all doses of oxprenolol (0.01, 0.03 and 0.1 mmol/kg) significantly lowered the blood pressure of SHAD-rats, the maximum response being produced within the first 2 h (Figure 5b); complete or partial recovery occurred during the 3 to 4 h period. Oxprenolol had no significant effect on heart rate in either animal model (Figure 5c and d).

(±)-Propranolol In SH-rats (±)-propranolol, 0.01, 0.03 and 0.1 mmol/kg s.c., evoked dose-dependent increases in blood pressure and falls in heart rate 1 h after dosing. Although blood pressure rapidly returned to, and fell below, pre-dosing levels after the two lower doses, the pressor response to 0.1 mmol/kg propranolol took 5 h to disappear (Figure 6a). The statistically significant bradycardia produced by propranolol, 0.03 mmol/kg, was transient (1 h) but that to 0.1 mmol/kg was slightly more prolonged (1 to 2 h) (Figure 6c).

In SHAD-rats, blood pressure was unchanged by propranolol at 1 h. During the 2 to 5 h period, however, blood pressure progressively declined and the anti-hypertensive response was independent of dose (Figure 6b). The bradycardia evoked by each dose of propranolol in SHAD-rats was maximal at 1 h after dosing and the effect of the highest dose persisted throughout the 5 h recording period (Figure 6d).

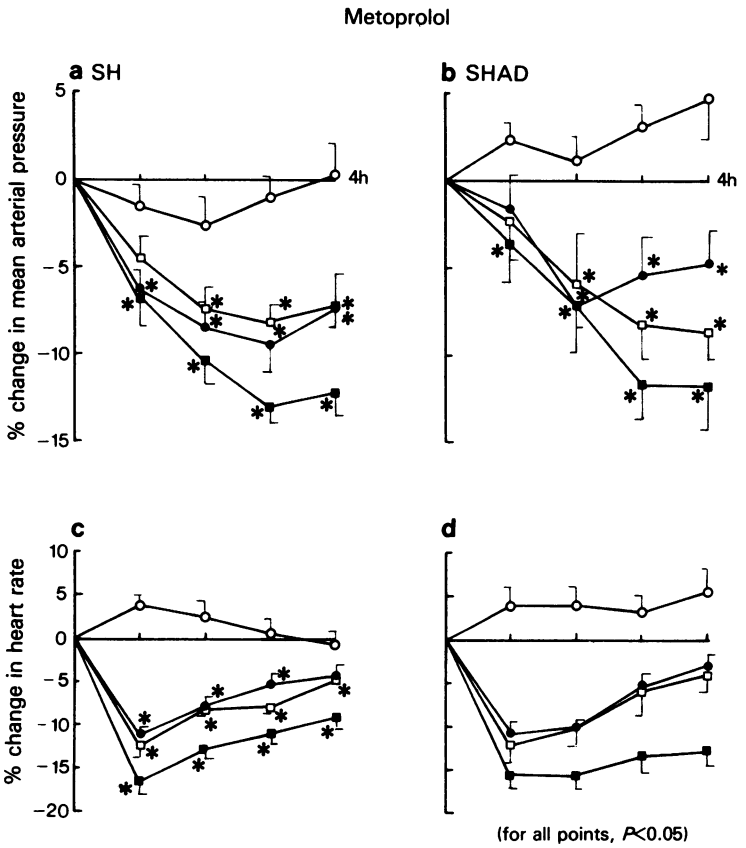

Figure 2 Effect of metoprolol on mean arterial pressure and heart rate in SH- and SHAD-rats; 0.01 mmol/kg (●), 0.03 mmol/kg (□), 0.1 mmol/kg (■) s.c. or control vehicle (○). Vertical bars show s.e. mean; $n = 14$ or 15 rats; * show significant ($P < 0.05$) differences between treated groups and control group. In SH-rats the basal mean blood pressure and heart rate of each group were, respectively, for metoprolol 0.01 mmol/kg, 143 ± 4 mmHg and 350 ± 7 beats/min; for 0.03 mmol/kg, 144 ± 4 mmHg and 339 ± 10 beats/min; for 0.1 mmol/kg, 143 ± 4 mmHg and 341 ± 7 beats/min; and for the control group, 142 ± 5 mmHg and 335 ± 8 beats/min. In SHAD-rats the corresponding figures were as follows: for metoprolol 0.01 mmol/kg, 142 ± 3 mmHg and 319 ± 6 beats/min; for 0.03 mmol/kg, 143 ± 3 mmHg and 309 ± 6 beats/min; for 0.1 mmol/kg, 144 ± 3 mmHg and 324 ± 8 beats/min; and for the control group, 143 ± 3 mmHg and 307 ± 4 beats/min.

(−)-Propranolol In SHAD-rats, (−)-propranolol tended to raise blood pressure initially, although the only significant pressor response was recorded 1 h after administration of 0.03 mmol/kg s.c. The anti-hypertensive response which followed the initial pressor phase was inversely related to dose. Thus, whereas (−)-propranolol, 0.01 mmol/kg, progressively reduced blood pressure during the 3 to 5 h period, 0.1 mmol/kg did not evoke a significant response (Figure 7a). The bradycardia associated with each dose of (−)-propranolol was rapid in onset (1 h) and persistent, although the response to 0.1 mmol/kg markedly diminished during the course of the experiment (Figure 7c).

(+)-Propranolol In SHAD-rats, only the highest dose of (+)-propranolol (0.1 mmol/kg s.c.) caused a transient fall in blood pressure (1 h) with a concomitant fall in heart rate (Figure 7b and d).

Discussion

The results of the present study indicate that the anti-hypertensive effects of a range of both relatively cardio-selective and non-selective β-adrenoceptor blocking drugs can be demonstrated after adrenal-demedullation in adult, female SH-rats. Furthermore, significant anti-hypertensive responses were not invariably

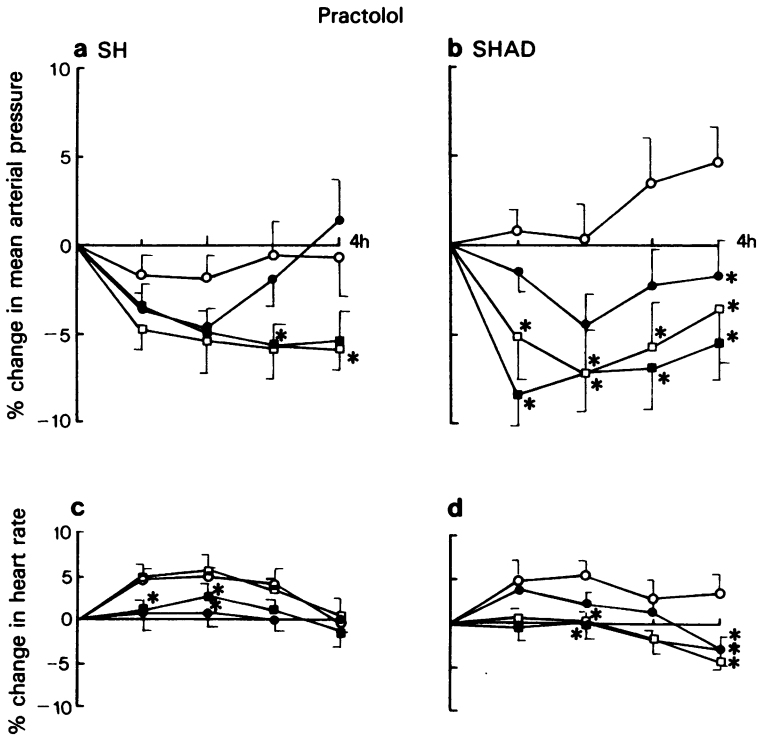

Figure 3 Effect of practolol on mean arterial pressure and heart rate in SH- and SHAD-rats; 0.01 mmol/kg (●), 0.03 mmol/kg (□), 0.1 mmol/kg (■) i.p. or control vehicle (○). Vertical bars show s.e. mean; $n = 15$ rats; * show significant ($P < 0.05$) differences between treated groups and control group. In SH-rats, the basal mean blood pressure and heart rate of each group were, respectively, for practolol 0.01 mmol/kg, 145 ± 4 mmHg and 355 ± 10 beats/min; for 0.03 mmol/kg, 144 ± 3 mmHg and 347 ± 8 beats/min; for 0.1 mmol/kg, 144 ± 4 mmHg and 351 ± 8 beats/min; and for the control group, 145 ± 4 mmHg and 336 ± 7 beats/min. In SHAD-rats, the corresponding figures were as follows: for practolol 0.01 mmol/kg, 144 ± 4 mmHg and 333 ± 7 beats/min; for 0.03 mmol/kg, 145 ± 4 mmHg and 342 ± 8 beats/min; for 0.1 mmol/kg, 143 ± 4 mmHg and 344 ± 6 beats/min; and for the control group, 143 ± 4 mmHg and 325 ± 9 beats/min.

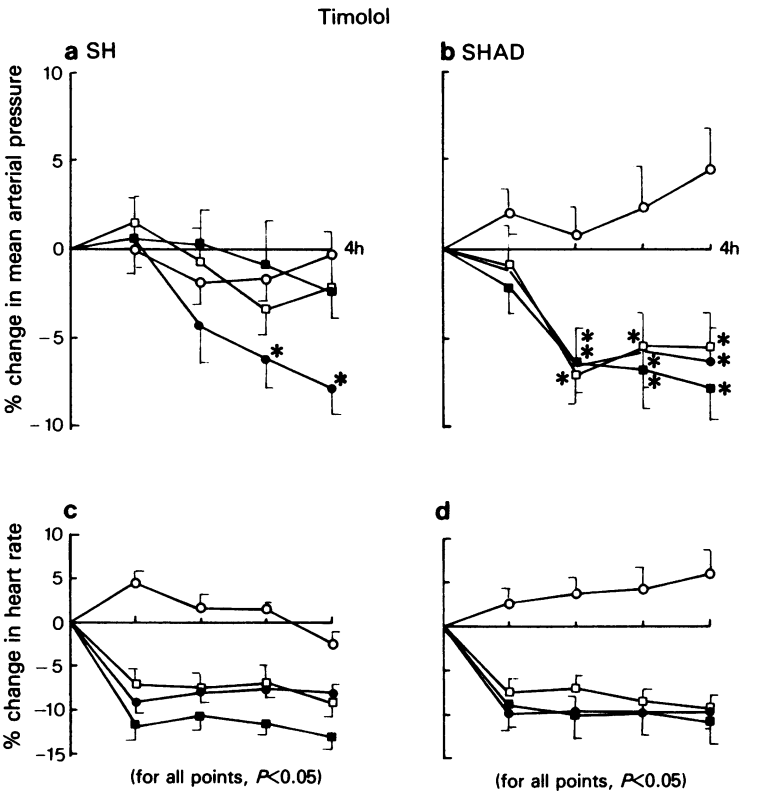

Figure 4 Effect of timolol on mean arterial pressure and heart rate in SH- and SHAD-rats; 0.01 mmol/kg (●), 0.03 mmol/kg (□), 0.1 mmol/kg (■) s.c. or control vehicle (○). Vertical bars show s.e. mean; $n = 14$ or 15 rats; * show significant ($P < 0.05$) differences between treated groups and control group. In SH-rats the basal mean blood pressure and heart rate of each group were, respectively, for timolol 0.01 mmol/kg, 139 ± 3 mmHg and 348 ± 6 beats/min; for 0.03 mmol/kg, 139 ± 4 mmHg and 353 ± 10 beats/min; for 0.1 mmol/kg; 138 ± 3 mmHg and 361 ± 5 beats/min; and for the control group 138 ± 3 mmHg and 347 ± 5 beats/min. In SHAD-rats the corresponding figures were as follows: for timolol 0.01 mmol/kg, 143 ± 4 mmHg and 322 ± 6 beats/min; for 0.03 mmol/kg, 142 ± 3 mmHg and 310 ± 6 beats/min; for 0.1 mmol/kg, 143 ± 4 mmHg and 322 ± 9 beats/min; and for the control group, 143 ± 3 mmHg and 309 ± 7 beats/min.

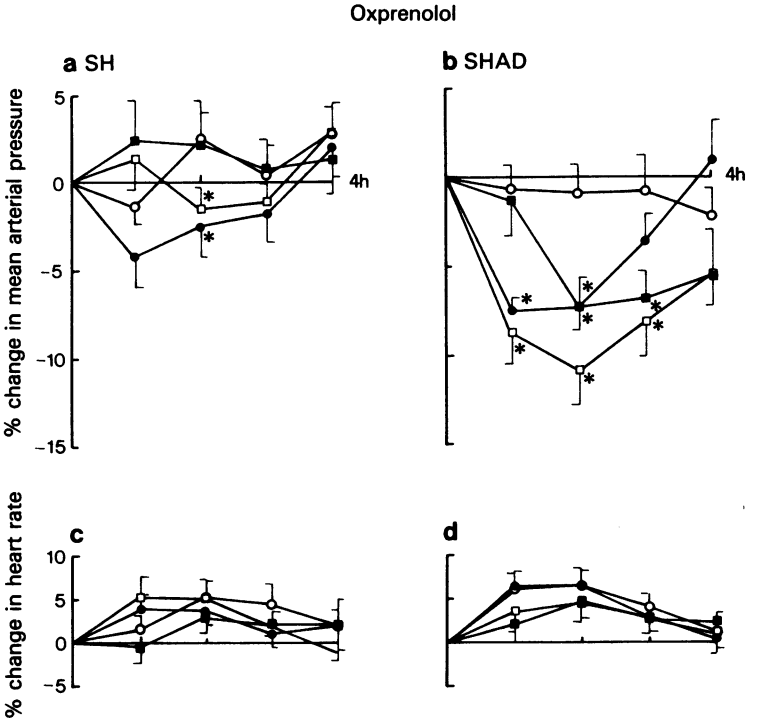

Figure 5 Effect of oxprenolol on mean arterial pressure and heart rate in SH- and SHAD-rats; 0.01 mmol/kg (●), 0.03 mmol/kg (□), 0.1 mmol/kg (■) i.p. or control vehicle (○). Vertical bars show s.e. mean; $n = 14$ or 15 rats; * show significant ($P < 0.05$) differences between treated groups and control group. In SH-rats, the basal mean blood pressure and heart rate of each group were, respectively, for oxprenolol 0.01 mmol/kg, 137 ± 4 mmHg and 336 ± 6 beats/min; for 0.03 mmol/kg, 136 ± 3 mmHg and 349 ± 10 beats/min; for 0.1 mmol/kg, 138 ± 4 mmHg and 336 ± 6 beats/min; and for the control group, 138 ± 4 mmHg and 338 ± 7 beats/min. In SHAD-rats the corresponding figures were as follows: for oxprenolol 0.01 mmol/kg, 145 ± 3 mmHg and 326 ± 7 beats/min; for 0.03 mmol/kg, 146 ± 3 mmHg and 334 ± 8 beats/min; for 0.1 mmol/kg, 145 ± 4 mmHg and 340 ± 7 beats/min; and for the control group, 144 ± 5 mmHg and 332 ± 8 beats min.

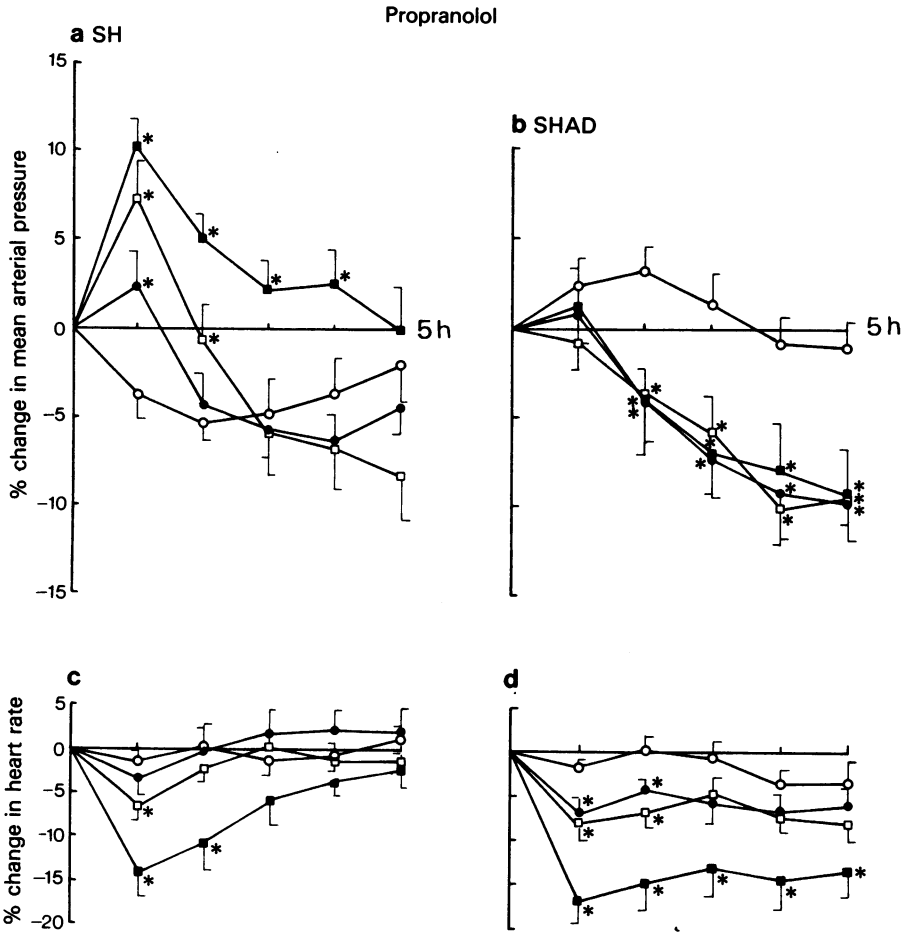

Figure 6 Effect of (±)-propranolol on mean arterial pressure and heart rate in SH- and SHAD-rats; 0.01 mmol/kg (●), 0.03 mmol/kg (□), 0.1 mmol/kg (■) s.c. or control vehicle (○). Vertical bars show s.e. mean; $n = 14$ or 15 (SH) or 10 (SHAD) rats; * show significant ($P < 0.05$) differences between treated groups and control group. In SH-rats the basal mean blood pressure and heart rate of each group were, respectively, for (±)-propranolol 0.01 mmol/kg, 151 ± 4 mmHg and 347 ± 12 beats/min; for 0.03 mmol/kg, 151 ± 5 mmHg and 336 ± 6 beats/min; for 0.1 mmol/kg, 155 ± 4 mmHg and 329 ± 9 beats/min; and for the control group, 152 ± 4 mmHg and 344 ± 8 beats/min. In SHAD-rats the corresponding figures were as follows: for (±)-propranolol 0.01 mmol/kg, 160 ± 4 mmHg and 331 ± 5 beats/min; for 0.03 mmol/kg, 160 ± 4 mmHg and 338 ± 7 beats/min; for 0.1 mmol/kg, 163 ± 5 mmHg and 353 ± 8 beats/min; and for the control group, 162 ± 4 mmHg and 334 ± 7 beats/min.

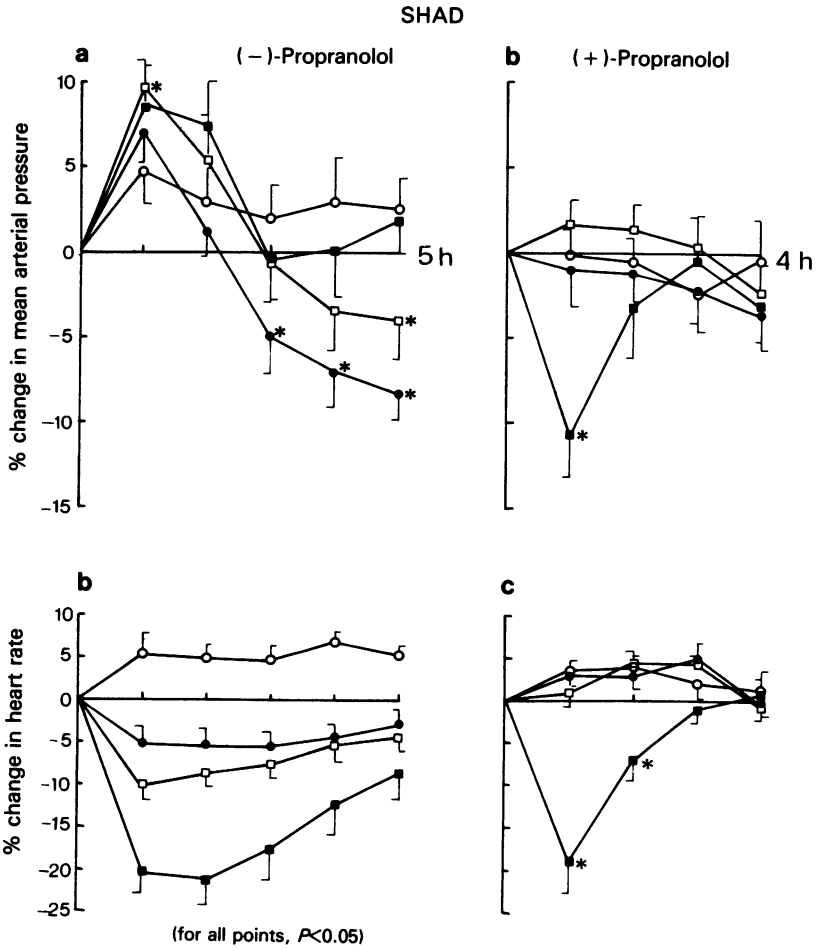

Figure 7 Effect of (−)- and (+)-propranolol on mean arterial pressure and heart rate in SHAD-rats; 0.01 mmol/kg (●), 0.03 mmol/kg (□), 0.1 mmol/kg (■) s.c. or control vehicle (○). Vertical bars show s.e. mean; $n \pm 14$ or 15 rats; * show significant ($P < 0.05$) differences between treated groups and control group. The basal mean blood pressure and heart rate of each group were, respectively, for (−)-propranolol 0.01 mmol/kg, 149 ± 4 mmHg and 311 ± 7 beats/min; for 0.03 mmol/kg, 146 ± 3 mmHg and 308 ± 4 beats/min; for 0.1 mmol/kg, 148 ± 3 mmHg and 305 ± 6 beats/min; and for the control group, 147 ± 3 mmHg and 297 ± 6 beats/min. The corresponding figures for (+)-propranolol were as follows; for 0.01 mmol/kg, 150 ± 5 mmHg and 347 ± 7 beats/min; for 0.03 mmol/kg, 152 ± 4 mmHg and 354 ± 8 beats/min; for 0.1 mmol/kg, 153 ± 5 mmHg and 365 ± 7 beats/min; and for the control group, 149 ± 6 mmHg and 351 ± 10 beats/min.

associated with significant reductions in heart rate, suggesting that these effects are not interdependent. Even in instances where a marked bradycardia was produced (e.g. with metoprolol, atenolol, timolol and high doses of (±)-propranolol), this effect was established before the maximum fall in blood pressure occurred. In the case of oxprenolol, and at low doses of (±)-propranolol, the blood pressure response was evoked in the absence of a change in heart rate.

(+)-Propranolol, which does not possess antihypertensive activity in man (Waal-Manning, 1970; Rahn, Hawlina, Kersting & Planz, 1974), also proved to be devoid of this activity in SHAD-rats at doses (0.01, 0.03 mmol/kg) which were effective for the racemate. The initial, transient, fall in blood pressure produced by the highest dose of (+)-propranolol was mirrored by a reduction in heart rate, suggesting that the blood pressure response was a consequence of myocardial depression. This latter effect is probably a manifestation of the membrane stabilizing (or 'quinidine-like') activity of the drug molecule (Howe & Shanks, 1966). The fact that there was no equivalent

transient decrease in blood pressure following administration of the racemate, and that membrane stabilizing activity is a property shared by both isomers of propranolol, is explained by the intrinsic pressor activity of (−)-propranolol in the SHAD-rat; the mechanism of this pressor response, in the absence of adrenal medullary catecholamines, is not yet understood.

The results of the present investigation indicate that adrenal catecholamine secretion plays a major role in masking the anti-hypertensive effects of some β-adrenoceptor blocking drugs, notably those without relative β_1-adrenoceptor selectivity (i.e. timolol, oxprenolol and propranolol). That (±)-propranolol produced a significant rise in the blood pressure of SH-rats suggests that this drug provokes an excessive secretion of adrenal catecholamines. It is probable that the masking action is mediated by the vasoconstrictor action (at peripheral α-adrenoceptors) of circulating catecholamines in the presence of vascular β_2-adrenoceptor blockade. This hypothesis is supported by the fact that atenolol, metoprolol, practolol (relatively β_1-adrenoceptor selective) and a low dose of timolol (and to a lesser extent, oxprenolol) exhibited anti-hypertensive activity in both SH- and SHAD-rats. In each of these situations the degree of vascular β_2-adrenoceptor blockade would be expected to be of a low order. It is also probable that recording of blood pressure directly, with the animals placed in a quiet rather than in a stressful environment (as is generally found when systolic blood pressure is determined indirectly by means of an inflatable tail cuff), would contribute towards minimising secretion of adrenal catecholamines and hence their circulatory consequences. Chiueh & Kopin (1978) have found that in SH-rats, plasma catecholamine levels are higher during indirect, than direct, measurement of blood pressure.

Finally, with respect to the SHAD-rat model itself, the blood pressure of these animals, following regeneration of the solitary adrenal cortex, is similar to that found in intact (SH) rats (see figure legends for basal blood pressure data). This observation is consistent with the results of studies by Skelton (1956), who demonstrated that adrenal regeneration hypertension occurs only in rats whose drinking water is replaced by saline.

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