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Prolonged protective effects following propranolol withdrawal against isoproterenol-induced myocardial infarction in normotensive and hypertensive rats

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Summary. Young adult, male and female, normotensive Sprague-Dawley (S-D) and spontaneously hypertensive rats (SHR) were injected with propranolol three times daily for 3 weeks. None of the animals manifested signs of withdrawal when the injections were terminated. Seven days later, the animals were challenged with a dose of isoproterenol which would produce massive myocardial infarction and 50–60% mortality in non-treated animals. The propranolol pretreatment caused marked tranquilizing and blood pressure lowering effects in SHR exclusively. Despite the 7-day propranolol withdrawal period, very few animals died and myocardial damage was minimal. However, blood pressure levels dropped to shock-like levels, blood CPK and LDH levels showed dynamic increases, there was marked hypertriglyceridaemia, and plasma corticosterone rose to supranormal levels. Microscopically, the hearts of the propranolol pretreated animals showed little evidence of necrosis but the SHR hearts manifested large atrial and ventricular thrombi. It is suggested that in the rat, propranolol treatment causes positive myocardial protective effects mediated through hormonal and metabolic changes and propranolol withdrawal does not lead to hypersensitivity to catecholamines. In fact, the beta-blocking effects of propranolol remain effective for some time after withdrawal.

Keywords: hypertension, propranolol, isoproterenol, myocardial infarction

Propranolol hydrochloride is a potent beta-adrenergic blocking agent that is effective in alleviating angina, as a hypotensive agent, as therapy for cardiac arrhythmias, as a tranquilizing agent, and is currently being tested as a preventative against recurrence of myocardial infarction (Shand 1975; NHLBL Report 1982). Some concern has been expressed that patients being treated with beta-blockers may suffer withdrawal symptoms ranging from palpitation, headache, angina, tachycardia, to myocardial infarction and sudden death. Hypersensitivity of beta-adrenoreceptors, reactive increase in sympathetic nerve activity, increased production of tri-iodothyronin, and reduced oxyhaemoglobin dissociation are some of the mechanisms proposed to explain the symptoms and complications which attend this withdrawal phenomenon (Nattel *et al.* 1979; Lindenfeld *et al.* 1980; Bolli *et al.* 1981).

The experimental models used for this study are uniquely well suited to test some of the above clinical problems and hypotheses:

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(a) spontaneously hypertensive rats (SHR) that develop high blood pressure in a manner which resembles essential hypertension as it occurs in man and which responds to the anti-hypertensive effects of propranolol (Wexler & McMurtry 1981), and (b) normotensive Sprague-Dawley (S-D) rats and hypertensive SHR that develop myocardial infarcts when challenged with the potent beta-adrenergic stimulating agent, isoproterenol (Wexler 1973, 1979) and reflect the pathophysiology of pre-existing normal blood pressure and hypertension on the outcome of an acute myocardial infarct.

The term 'myocardial infarction' is used instead of 'myocardial necrosis' because the pathophysiologic conditions of our experimental models are best equated with myocardial ischaemia. Large doses of isoproterenol are used to cause intense stimulation of beta-adrenergic activity. Under these conditions, rats develop a spectrum of pathophysiologic changes which mimic ischaemic myocardial infarction in humans, i.e., dynamic changes in serum enzymes (CPK, SGOT, SGPT and LDH), temporary abnormal glucose tolerance, great excursions of aldosterone and corticosterone, congestive heart failure, and hypotensive shock. The intense increase in cardiac output concomitant with greatly lowered peripheral resistance overwhelms the capacity of the coronary arteries, albeit patent, to provide sufficient blood to sustain myocardial need for energy. Ischaemia and infarction supervene. The histopathology of these myocardial infarcts is identical to those that occur spontaneously in arteriosclerotic rats and in SHR. Most importantly, ECG tracings of rat hearts during isoproterenol-induced myocardial infarction are identical to ECG tracings of humans having myocardial infarction due to ischaemia.

Sprague-Dawley rats were used as the normotensive counterparts of the hypertensive SHR because the author has extensive experience (and data) pertinent to isoproterenol-induced myocardial infarction in this strain. Wistar–Kyoto rats (WKy) recommended by some as the counterpart of SHR, often have blood pressures bordering on the hypertensive level and vary considerably in their physiological parameters (e.g., blood pressure and chemistry) from shipment to shipment.

To stimulate the clinical conditions associated with propranolol withdrawal, normotensive S-D rats and hypertensive SHR were injected with propranolol three times per day for 3 weeks; the injections were then stopped and the animals were observed for 7 days for evidence of withdrawal. They were then challenged with isoproterenol to produce myocardial infarction. The purpose of this experimental protocol was to compare the blood pressure lowering effectiveness of propranolol in normotensive (S-D) rats with that in hypertensive (SHR) rats, to determine whether hypertensive and normotensive rats would differ in their response to propranolol withdrawal, and whether the pathophysiologic response pattern which attends isoproterenol-induced myocardial infarction would be palliated or exacerbated in hypertensive and/or normotensive rats pretreated with propranolol.

Methods

All of the animals used in this experiment were from the author's animal research breeding colony and were highly inbred by many generations of brother:sister matings. The SHR were derived from the original spontaneously hypertensive rats developed by the Japanese (Okamoto & Aoki 1963) and were kindly provided by Dr Carl T. Hansen, NIH, Bethesda, Maryland. SHR develop progressively increasing blood pressure shortly after weaning and stable high blood pressure of 200 ± 10 mmHg is reached by 7–8 months of age. In order to test hypertensive animals while their blood pressure is rising steeply but while they are still free of hypertensive-related lesions, 6-month-old SHR and normotensive S-D rats were used.

Male ($n = 150$) and female ($n = 150$) SHR, and male ($n = 150$) and female ($n = 150$) S-D

were selected randomly and divided into control and experimental groups. Large numbers of animals were used to ensure an adequate number of survivors during the acute stages of an isoproterenol-induced myocardial infarction. At the outset of the experiment, non-treated hypertensive male ($n=10$) and female ($n=10$) SHR and normotensive male ($n=10$) and female ($n=10$) S-D rats were autopsied as baseline controls. All remaining rats were injected with 1.0 mg/100 g body wt of D-l-propranolol (l-isopropylamino)-3-(l-naphthyloxy)-2-propranolol hydrochloride, Ayerst Laboratories, Inderal, suspended in sterile water and administered s.c, three times per day for 3 weeks. Propranolol injections were then terminated and the animals were observed for evidence of propranolol withdrawal for 7 days. Representative numbers of animals ($n=10$) of each of the four groups were killed at 4 and 8 days after propranolol withdrawal. All remaining animals were injected twice on 2 consecutive days with a high dose (50 mg/100 g body wt, s.c.) of isoproterenol (1-(3,4-dihydroxyphenyl)-2 isopropyl amino ethanol hydrochloride) Winthrop Laboratories, Isuprel suspended in saline. This dose had been shown to produce massive myocardial infarction in S-D and SHR with a 40–50% survival rate (Wexler 1979). Representative numbers ($n=10$) of each of the four groups were killed 4 h after the first (day 1) and second (day 2) injection of isoproterenol, on day 3 when myocardial necrosis is on-going, and on days 8, 10 and 15 (after isoproterenol) during the myocardial repair phase. At the close of the experiment, non-treated hypertensive male ($n=10$) and female ($n=10$) SHR, and non-treated normotensive male ($n=10$) and female ($n=10$) S-D rats were killed to determine what changes had occurred in the various parameters measured during the 40-day interim of the experiment. These control animals were 220 days old. To check the batch potency of isoproterenol to produce acute myocardial infarction, 6-month-old male SHR ($n=30$) and S-D rats ($n=30$) were injected with the same doses of isoproterenol given to the propranolol pretreated animals. These animals were autopsied in equal numbers ($n=10$ SHR, $n=10$ S-D) on days 1 and 2, 4 h after isoproterenol.

The animals had access to food (Purina Rat Chow) and water *ad libitum*. Light, humidity, and temperature were monitored. Systolic blood pressure of each animal was taken before autopsy using the Friedman:-Freed indirect microphonic manometer under light Seconal anaesthesia. Blood samples were taken from each animal, centrifuged (refrigerated) and analysed using an Auto-Analyzer (Technicon) for creatine phosphokinase (CPK), lactic dehydrogenase (LDH), triglycerides, and total cholesterol. Plasma corticosterone levels were determined by radioimmunoassay (Iams *et al.* 1979). At necropsy, record was made of the presence, severity, or absence of myocardial infarction for each animal. Key organs, e.g., adrenal and thymus glands, were trimmed of excess tissue and weighed for gravimetric analysis. Organs were fixed in neutral formalin for histopathology. Analysis of variance and bio-statistical analyses of all data followed the procedures and tables cited by Snedecor (1967).

Results

General observations

Propranolol treatment produced striking tranquilization of the SHR with no obvious effects on the S-D rats. During the 8-day withdrawal period, the SHR manifested a slight resurgence of their characteristic hyperkinetic behaviour, but otherwise there were no untoward signs of withdrawal except in the case of male SHR. All male SHR autopsied 4 days after propranolol withdrawal had copious quantities of ascitic fluid but this was not found in male SHR autopsied 8 days after propranolol withdrawal. During the acute stages of myocardial infarction (days 1 and 2), the SHR had symptoms of severe dyspnoea. There was no evidence of

the anuria (followed later by diuresis), tachycardia, and profound prostration which characteristically attends isoproterenol-induced massive myocardial infarction in S-D and SH rats. During the acute myocardial necrosis phase (days 1 to 3), the normotensive S-D rats produced 1 to 3 ml of thoracic fluid (S-D usually accumulated 8–11 ml of thoracic fluid when subjected to this dose of isoproterenol). The hydrothorax condition disappeared during the myocardial repair phase (days 4 to 15). In direct contrast, there was no sign of congestive heart failure in SHR which usually exhibit severe congestive heart failure during the myocardial repair phase. None of the 90 male S-D and 90 SHR died; two of the 90 female S-D died but 13 of the 90 female SHR succumbed between days 3 and 15, i.e., the myocardial repair phase. The group of male S-D ($n=30$) and SHR ($n=30$) that were injected with isoproterenol exclusively and killed 4 h later on days 1 and 2 became prostrate, developed severe hydrothorax and grossly visible myocardial infarcts involving all of the apex and left ventricle. This ancillary group was used to confirm the myocardial infarct-inducing potency of the isoproterenol used in the main experiment.

Systolic blood pressure

Although the progressively rising blood pressure of these 6-month-old SHR reached

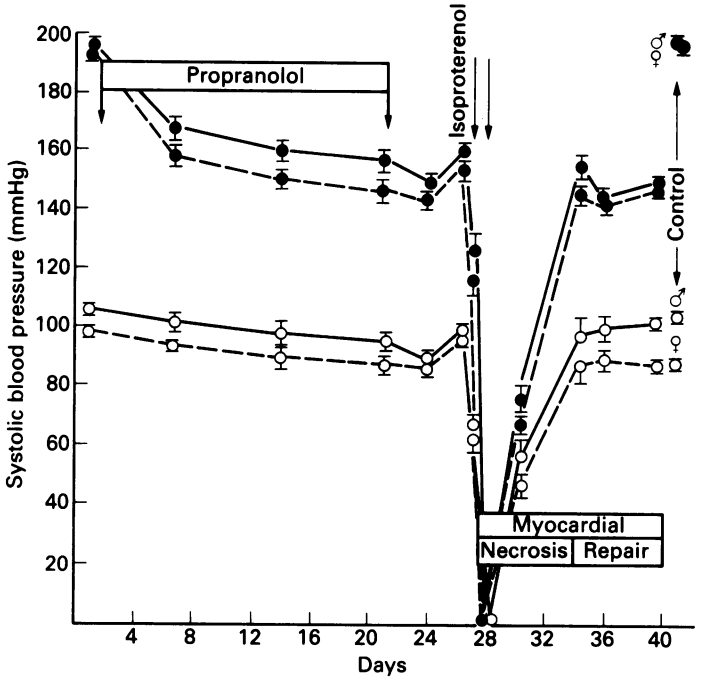

Fig. 1. Changes in the systolic blood pressure levels of young adult, male (—) and female (---), normotensive Sprague-Dawley (○) and spontaneously hypertensive rats (SHR) (●) following 3 weeks treatment with propranolol (three times per day). After a 7-day withdrawal period, two injections of isoproterenol were given, spaced 24 h apart (days 1 and 2). Animals were also killed on day 3 after isoproterenol (when myocardial necrosis ordinarily occurs) and on days 8, 10 and 15 after isoproterenol (when myocardial repair would occur). Control animals were killed before propranolol treatment and at the close of the experiment to account for any changes during the 40-day extent of the experiment. Each point depicted is the mean ± standard error; a minimum of $n=10$ for each of the points shown. This same protocol was followed for Figs 2 through 6.

190±10 mmHg, propranolol injections elicited a prompt and statistically significant ($P<0.001$) reduction in blood pressure (Fig. 1). Despite discontinuance of propranolol, the blood pressure levels of SHR continued the downward trend with a slight rise on day 8 after withdrawal (Fig. 1). The blood pressure of the normotensive S-D rats were reduced gradually during the propranolol treatment, showing a similar dip followed by a slight increase in blood pressure during the period of propranolol withdrawal.

During the acute myocardial necrosis phase (days 1 and 2), the blood pressures of S-D and SHR dropped precipitously reaching barely detectable levels, then rose to levels between 40 and 90 mmHg on day 3. They returned to control levels in S-D rats but only to reduced blood pressure levels, produced by the earlier propranolol treatment, in SHR, i.e., 149±2 mmHg (Fig. 1).

Enzymes

Creatine phosphokinase (CPK). Blood CPK levels rose progressively during the 3 weeks of propranolol treatment. This progressive rise was marked ($P<0.001$) in the normotensive S-D rats with only gradually rising levels in SHR (Fig. 2). During the period of propranolol withdrawal, CPK levels dropped ($P<001$) in S-D rats and there was no significant change in CPK levels in SHR (Fig. 2). Injection of isoproterenol elicited dynamic increases ($P<0.001$) in CPK activity with greater increases in CPK levels in S-D than in SHR (Fig. 2). During the myocardial repair phase, CPK levels in all animals were restored to normal (Fig. 2).

Lactic dehydrogenase (LDH). Blood LDH levels rose gradually in all animals during the period of chronic treatment with propranolol, and rose sharply in all animals following propranolol withdrawal (Fig. 3). The induction of acute myocardial necrosis elicited increases ($P<0.001$) in LDH activity in S-D and SH rats (Fig. 3). Although the pattern of LDH change was erratic in S-D rats, its general upward trend during the myocardial repair phase was progressive, culminating at levels considerably ($P<0.001$) above normal, whereas blood LDH levels fell toward normal levels in SHR (Fig. 3).

Lipids

Triglycerides. The SHR were characteristically hyperlipidaemic (Fig. 4). Both SHR and S-D rats showed little change in triglyceride levels during the periods of propranolol treatment and withdrawal (Fig. 4). The S-D rats had considerable hypertriglyceridemia ($P<0.001$) in response to isoproterenol, concomitant with slight increases in SHR. Circulating triglyceride levels promptly fell to normal in all animals during the myocardial repair phase (Fig. 4).

Total cholesterol. Circulating cholesterol levels followed the same pattern as triglycerides except that there were no statistically significant increases in cholesterol levels during the acute myocardial necrosis phase in S-D or SHR.

Steroids

Corticosterone. Blood corticosterone levels declined steadily ($P<0.001$) in male and female SHR during propranolol treatment; concomitantly, male S-D rats showed lowered levels ($P<0.001$) (Fig. 5). There was a further dichotomous drop in blood corticosterone in S-D rats following propranolol withdrawal, in direct contrast to a considerable increase ($P<0.001$) in corticosterone levels in SHR (Fig. 5). During acute myocardial infarction (days 1 and 2), the corticosterone levels rose to above normal levels in S-D rats with a similar large rise in female SHR but a significantly reduced ($P<0.001$) response in male SHR (Fig. 5). All animals showed progressive reduction of corticosterone secretion with progressive myocardial repair (Fig. 5).

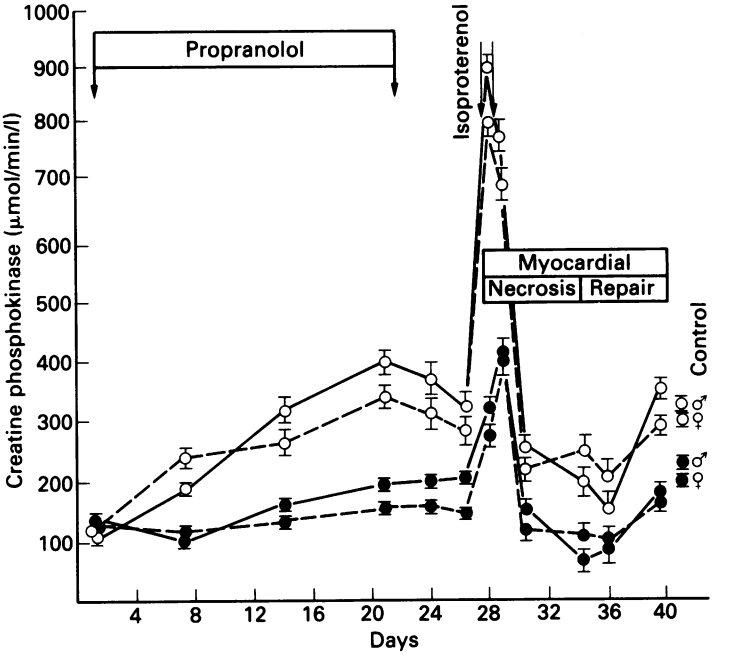

Fig. 2. Changes in blood creatine phosphokinase levels (at 37°C). Symbols and protocol as Fig. 1.

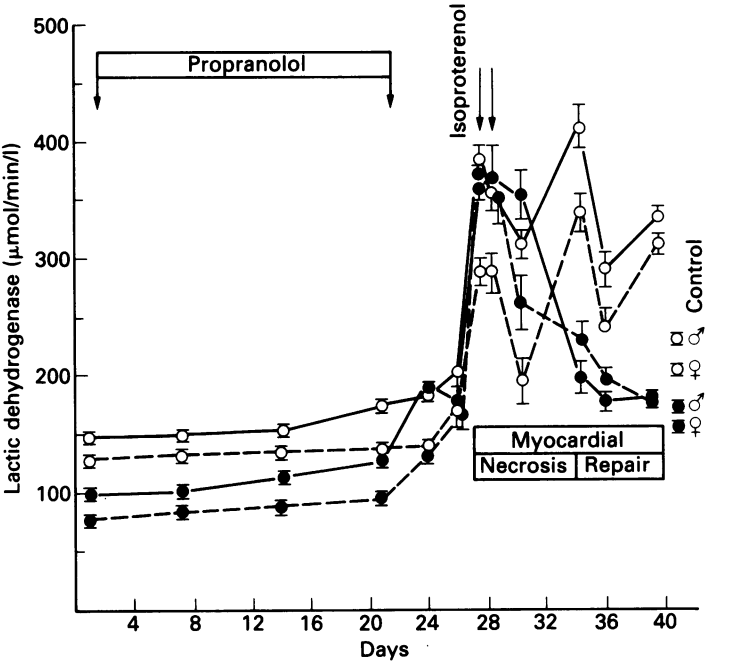

Fig. 3. Changes in blood lactic dehydrogenase levels (at 30°C). Symbols and protocol as Fig. 1.

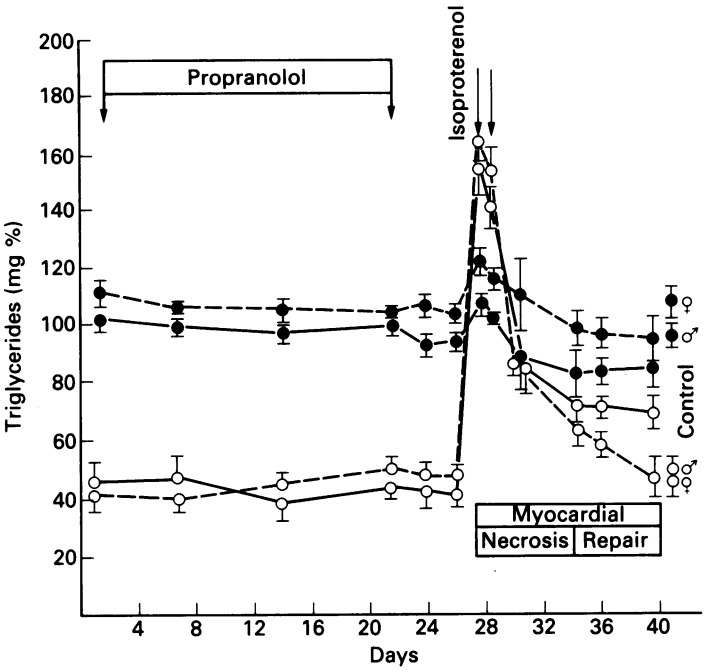

Fig. 4. Changes in blood triglyceride levels. Symbols and protocol as Fig. 1.

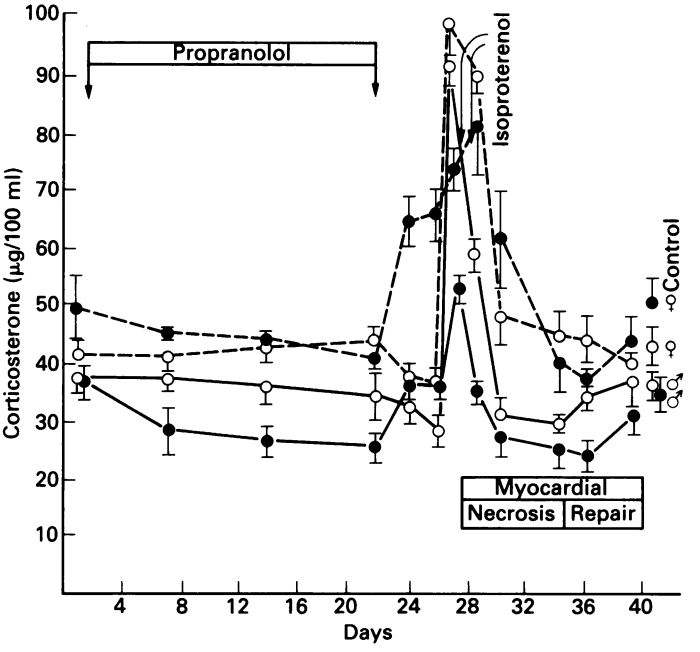

Fig. 5. Changes in blood corticosterone levels. Symbols and protocol as Fig. 1.

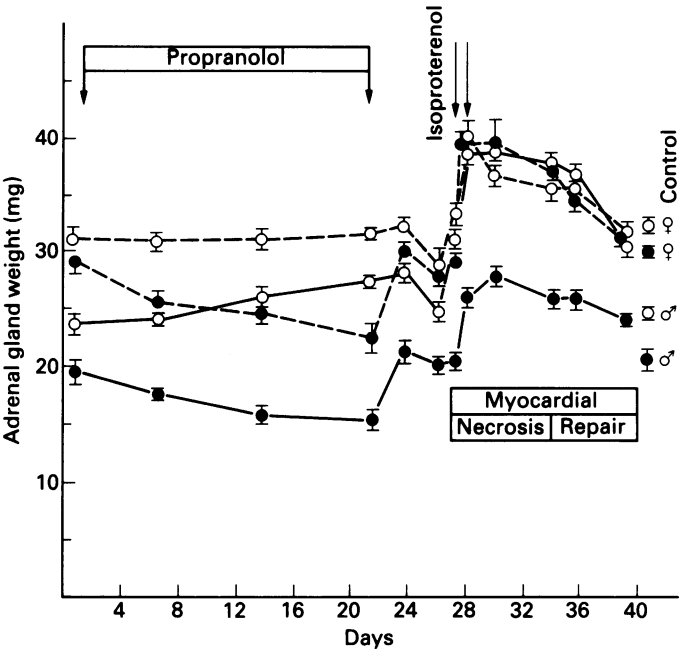

Fig. 6. Changes in adrenal gland weight. Symbols and protocol as Fig. 1.

Gravimetric observations

Changes in body weight. During the induction of an isoproterenol-induced myocardial infarct, rats normally show rapid loss of body weight . There were no statistically significant changes in body weight in any of the propranolol-treated animals.

Changes in heart and kidney weight. Heart and kidney weight also usually undergo rapid changes during an isoproterenol-induced myocardial infarct. There were no statistically significant changes in heart and kidney weights in these propranolol-treated animals.

Adrenal and thymus gland weight. The adrenal glands of SHR are characteristically smaller than those of most strains of normotensive rats (Fig. 6). (Female rats of all rodent strains have heavier adrenal glands than males.) The 21-day regimen of propranolol treatment caused a definite ($P<0.001$) fall in adrenal gland weight exclusively in SHR (Fig. 6). Propranolol withdrawal was followed by a significant ($P<0.001$) increase in adrenal glandular weight in SHR only (Fig. 6). Acute myocardial necrosis was associated with significant ($P<0.001$) increases in adrenal glandular weight in SHR and S-D rats. This condition of acute adrenal gland enlargement persisted throughout most of the myocardial necrosis and repair phases (days 1 to 15) (Fig. 6). During the period of propranolol treatment, the thymi of SHR increased in weight inversely to the reduction of adrenal gland weight. However, on days 1 and 2, the thymus glands of SHR and S-D rats became greatly enlarged concomitant with increased adrenal weight. During the myocardial necrosis and repair phase (days 3 through 15), the thymi of all animals became severely involuted (e.g., average thymus weight on days 1 and $2 = 564 \pm 15$ mg compared to 96 ± 11 mg on day 15 and 301 ± 9 mgs for 220 day old controls.

Gross and microscopic pathology

There was no gross or microscopic evidence of any pathology in any animal during chronic treatment with propranolol or following its abrupt withdrawal, except for the grossly-visible fatty liver condition in SHR. (Fatty infiltration of the liver and hyperlipidaemia are characteristic of the sub-strain of SHR bred in the author's animal research colony.) There was a remarkable absence of gross or microscopic pathology of the myocardium in the animals challenged with isoproterenol. A few animals (SHR and S-D rats) displayed grossly visible, apical infarcts with occasional foci of necrosis extending into the left ventricle. Histological examination confirmed the gross observations showing very mild WBC infiltration and interfascicular oedema (Fig. 7) in both SHR and S-D rats on days 1 and 2 of the acute necrosis phase. By days 3 to 10, the WBC infiltration and necrosis resolved completely. However, 12% of the male and 8% of the female SHR showed foci of moderate WBC infiltration and necrosis within the atria concomitant with atrial and ventricular thrombi (Fig. 8). The latter conditions resolved completely by day 10. Both the SHR and S-D rats showed fatty infiltration of the liver on days 1 and 2 but the hepatic lipid was completely resolved in the S-D rats by day 3. (The persistent fatty liver in SHR (days 3 to 10) is believed to be an inherent characteristic of this substrain of SHR.) Microscopic examination of the greatly enlarged thymus glands found during the acute myocardial phase showed that glandular enlargement was due to intense hyperplasia of thymocytes and oedema, but there

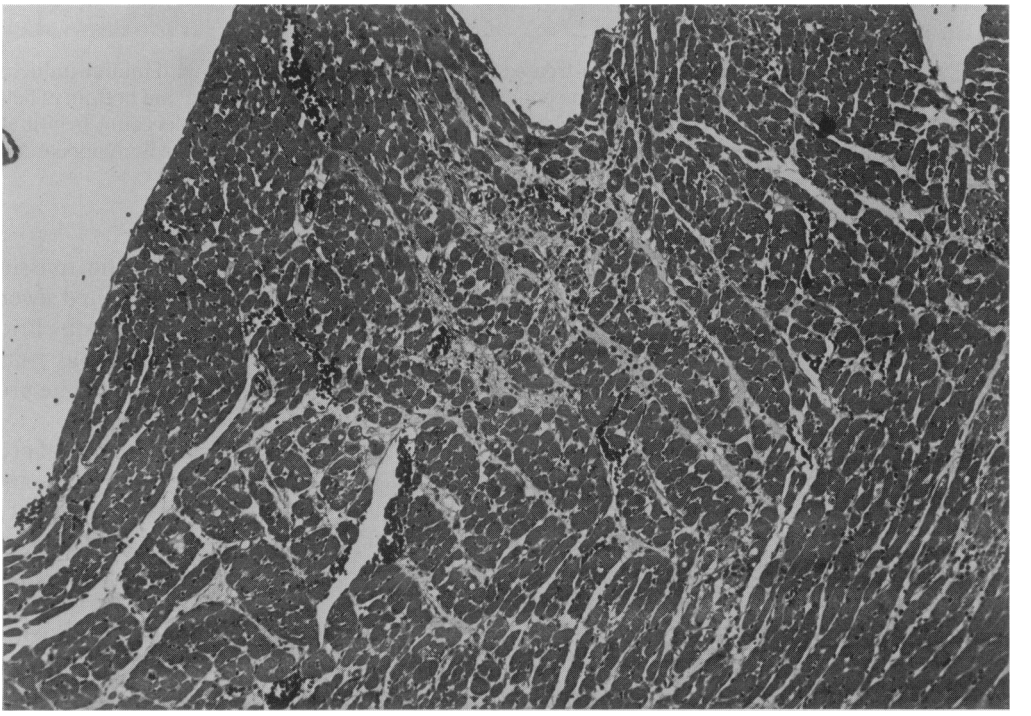

Fig. 7. Left ventricle of the heart of a S-D rat pre-treated with propranolol, challenged with infarct-inducing doses of isoproterenol, and autopsied on day 3. The myocardium shows slight interfascicular oedema (light grey in photo), little or no necrosis, and absence of WBC infiltration. H & E. × 110.

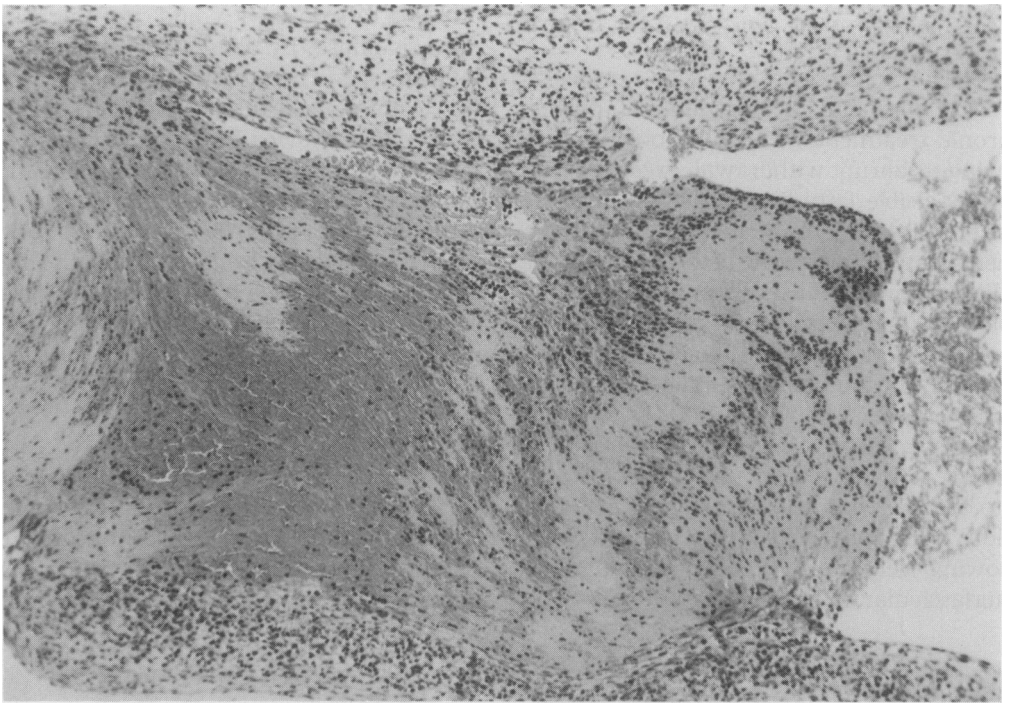

Fig. 8. Left ventricle of the heart of a SHR pre-treated with propranolol, challenged with infarct-inducing doses of isoproterenol, and killed on day 3. The endocardium of the left ventricle (top and bottom of field) shows necrosis and WBC infiltration with a large adherent, mural thrombus undergoing beginning organization. Despite aneurysmal dilatation of the left ventricle, the rest of the myocardium appeared to be in good condition. H & E. × 120.

was no fatty infiltration. The hyperplastic adrenal glands of both SHR and S-D rats (days 1 to 15) were haemorrhagic and all zones were intensely depleted of lipid. The histopathology of isoproterenol-induced myocardial infarction in SHR and S-D rats has been published (Wexler 1973, 1979).

Discussion

Propranolol appeared to be selective as an anti-hypertensive agent in that it caused more effective reduction of blood pressure in animals with pre-existing hypertension (SHR) than in normotensive (S-D) animals. There was little or no evidence of untoward changes due to propranolol withdrawal. Even 7 days after propranolol withdrawal, subsequent challenge with isoproterenol did not elicit the usual characteristic massive myocardial infarction with associated severe pathophysiologic sequelae and death. Prior propranolol treatment (followed by 7-day withdrawal) afforded virtually complete protection against myocardial infarction.

The anti-hypertensive effectiveness of propranolol in rodents has been the subject of some debate; some investigators claim that it is effective (Weiss *et al.* 1974; Takeda & Bunag 1980; Wexler & McMurtry 1981) while others have found it to be without effect (Nishiyama *et al.* 1978). Wexler & McMurty (1981) have shown that propranolol will reduce pituitary and adrenal gland weights, reduce secretion of aldosterone and corticosterone, and prevent the escalation of high blood pressure in SHR. It is suggested that the effective reduction of blood pressure

levels in this experiment was mediated by reduced pituitary–adrenal glandular activity as shown in particular by reduction of adrenal gland weight and corticosterone levels in SHR. Although the 3-week period of prior treatment with propranolol appeared to prevent effectively the myocardial infarct-inducing effects of isoproterenol, the blood pressures of all animals given isoproterenol fell to barely detectable levels. Thus, prior treatment with propranolol did not prevent the potent vasodilating effects of isoproterenol. Despite this shock-like condition, comparatively few animals died. It is of interest that the blood pressure of the genetically normotensive S-D rats was restored to normal during the myocardial repair phase but the blood pressure levels of the SHR were not restored to their usual severely elevated levels, i.e., 150 not 200 mmHg.

The liver plays a major role in determining the metabolic half-life of propranolol, which in man is 2–3 h and in animals is 24–48 h (Hayes & Cooper 1971; Shand 1975). The route of administration of propranolol is paramount to its rate of metabolism (Hayes & Cooper 1971; Shand 1975). Many experimentalists administer propranolol *per os* (Weiss 1974; Nishiyama *et al.* 1978; Takeda & Bunag 1980), whereas propranolol was administered subcutaneously three times daily to the animals in this experiment. This could account for propranolol's prolonged effectiveness in the current study despite its reputed short half-life.

The gradual increase in circulating CPK and LDH activity during the 3-week period of propranolol treatment is believed to be due to normal increases in enzyme activity which accompany maturation. Paradoxically the acute, and much greater, increase in CPK levels in S-D rats is in keeping with previous observations that hypertensive SHR are less susceptible to isoproterenol-induced myocardial infarction than normotensive S-D rats (Wexler 1979). The prolonged abnormal elevation of LDH levels in S-D rats during days 1 to 15 indicates that myocardial repair is more effective in SHR than in S-D rats.

Propranolol will block insulin release (Shand 1975), reduce circulating free fatty acid levels, and block the conversion of triglycerides to cholesterol (Lipson *et al* 1971; Shand 1975). Isoproterenol will cause great surges in circulating triglycerides and free fatty acids but not in cholesterol in rats during acute myocardial infarction (Wexler 1973, 1979). Although propranolol pretreatment caused no change in circulating lipid levels, the subsequent injection of isoproterenol caused a supernormal increase in triglyceride levels in the normotensive S-D rats but only a slight response in the SHR. Perhaps propranolol is more effective in blocking the metabolic response in hypertensive than in normotensive rats, and hypertensive rats are less responsive to isoproterenol.

Propranolol will cause reductions in circulating corticosterone and aldosterone levels as well as in adrenal gland weight commensurate with reduced blood pressure levels in SHR (Wexler & McMurtry 1981). In this experiment, only the SHR showed significantly reduced blood corticosterone and adrenal gland weight. There was a marked rise, or 'escape,' of corticosterone levels during the propranolol withdrawal period which, again, was found in SHR only. When the animals were challenged with isoproterenol, it was the normotensive S-D rats that manifested the greatest increase in circulating corticosterone levels concomitant with their greater sensitivity to the mycardial infarct-inducing effects of isoproterenol. The author believes that the acute adrenal gland hyperplasia, concomitant thymus gland involution, and supranormal corticosterone secretion during the acute cardiac necrosis phase are in keeping with intense activation of the pituitary–adrenal axis in response to the stress of severely reduced blood pressure. Survival of animals during the acute necrosis phase is believed to be commensurate with the capacity of the pituitary–adrenal axis to respond to the duress of acute myocardial necrosis (Wexler 1979). In this experiment as in all others, adrenal steroid secretion

becomes normalized during the myocardial repair phase. However, despite normalized adrenal secretory levels, adrenal hyperplasia and increased adrenal gland weight persists for a considerable time beyond the myocardial repair phase.

Although the protective effects of propranolol pretreatment against the necrosis-inducing effects of isoproterenol was remarkable, it is interesting that large ventricular thrombi and some cardiac necrosis appeared in SHR exclusively. Rats seldom develop thrombi. The high incidence of atrial and ventricular thrombi in these hypertensive SHR suggests that hypercoaguability is a concomitant of high blood pressure. Normotensive rats (S-D) made severely hypertensive will also develop left ventricular saccular aneurysms and thrombi when subjected to an acute myocardial infarction (Wexler 1974). The greatly hypertrophied hearts of SHR which serve to maintain cardiac compensation during the hypertensive state also contribute to the ultimate failure of the heart, i.e, aneurysm formation.

Acknowledgements

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References

Bolli P., Buhler F.R., Raeder E.A., Amanru F.W., Meier M., Rogg H., & Burckhardt D. (1981) Lack of beta-adrenoreceptor hypersensitivity after abrupt withdrawal of long-term therapy with oxprenolol. *Circulation* **64**, 1130–1134.

Hayes A. & Cooper R.G. (1971) Studies on the absorption, distribution, and excretion of propranolol in rat, dog, and monkey. *J. Pharmac. exp. Ther.* **176**, 302–311.

Iams S.G., McMurtry J.P. &Wexler, B.C. (1979) Aldosterone, deoxycorticosterone, corticosterone, and prolactin changes during the lifespan of chronically and spontaneously hypertensive rats. *Endocrinology* **104**, 1357–1363.

Lindenfeld J., Crawford M.H., O'Rourke R.A., Levine S.P., Montiel M., & Horwitz L.D. (1980) Adrenergic responsiveness after abrupt propranolol withdrawal in normal subjects and in patients with angina pectoris. *Circulation* **62**, 704–711.

Lipson M.J., Naimi S. & Prager S. (1971) Synergistic effect of propranolol and nicotinic acid on the inhibition of free fatty acid release in the dog. *Circ. Res.* **28**, 270–276.

NHLBL Report (1982) β-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. *JAMA* **247**, 1707–1714.

Nattel S., Rangno R.E. & Van Lorn G. (1979) Mechanism of propranolol withdrawal phenomena. *Circulation* **59**, 1158–1164.

Nishiyama K., Nishiyama A., Pfeffer M.A. & Frohlich E.D. (1978) Systemic and regional flow distribution in normotensive and spontaneously hypertensive young rats subjected to lifetime β-adrenergic receptor blockade. *Blood Vessels* **15**, 333–347.

Okamoto K. & Aoki K. (1963) Development of a strain of spontaneously hypertensive rats. *Jap. Circ. J.* **27**, 282–293.

Shand D.G. (1975) Propranolol. *N. Engl. J. Med.* **293**, 280–285.

Snedecor G.W. (1967) *Statistical Methods.* 6th edn. Cedar Falls: Iowa State College Press.

Takeda K. & Bunag, R.D. (1980) Chronic propranolol treatment inhibits sympathetic nerve activity and keeps blood pressure from rising in spontaneously hypertensive rats. *Hypertension* **1**, 228–235.

Weiss L., Lundgren Y. & Folkow B. (1974) Effects of prolonged treatment with adrenergic β-receptor antagonist on blood pressure, cardiovascular design, and reactivity in spontaneously hypertensive rats. *Acta Physiol. Scand.* **91**, 447–457.

Wexler B.C. (1973) Protective effects of propranolol on isoproterenol-induced myocardial infarction in arteriosclerotic and non-arteriosclerotic rats. *Atherosclerosis* **18**, 11–42.

Wexler B.C. (1974) Pathophysiologic effects of pre-existing hypertension on isoproterenol-induced myocardial infarction in arteriosclerotic and non-arteriosclerotic rats. *Atherosclerosis* **19**, 161–184.

Wexler B.C. (1979) Isoprenaline-induced myocardial infarction in spontaneously hypertensive rats (SHR). *Cardiovasc. Res.* **13**, 450–458.

Wexler B.C. & McMurtry J.P. (1981) Propranolol-induced alterations in the pathophysiology of spontaneously hypertensive rats. *Life Sci.* **29**, 1409–1416.