It is reasonable to conclude that the sustained cardiac acceleration following bretylium injection in the ganglioplegic dog is due to the continuous local action of norepinephrine. The prolonged duration of norepinephrine action after bretylium could be related to continuous release of norepinephrine or it could be related to inhibition of uptake of norepinephrine by the nerve endings (3,11), since the latter process is reported to be one of the important mechanisms of reducing levels of circulating catecholamine. Also, bretylium potentiates the effect of injected catecholamines (3,16), possibly by the same mechanism (3). In addition, bretylium has been reported to inhibit monoamine oxidase (17), therefore a decrease in the rate of inactivation of circulating catecholamines might be a factor in causing the prolonged increase in the heart rate.

Summary. Intravenous injection of 10 mg/kg of bretylium produced a sustained elevation of the heart rate in ganglioplegic dogs and in vagotomized spinal dogs and did not have this effect in reserpinized ganglioplegic dogs. At any time after bretylium injection the elevated heart rate could be reduced to the control level by injection of the beta adrenergic receptor-blocking agent, propranolol. The urinary norepinephrine output increased strikingly immediately after bretylium injection and then decreased to control levels, whereas the epinephrine output in the urine was not increased. On the basis of these results the tachycardia throughout the experiments could be attributed largely or entirely to the action of norepinephrine despite the inactivation of the cardioaccelerator pathway.

The author is greatly indebted to Dr. W. B. Youmans for his constructive criticism and advice in conducting these experiments and in the preparation of the manuscript and to Dr. H. Hift for kindly carrying out the determination of catecholamine. The author is grateful to Ayerst Laboratories for supplying the propranolol and to Burroughs Wellcome & Co. for supplying the bretylium.

1. Boura, A. L. A. and Green, A. F., Ann. Rev. Pharmacol. **5**, 183 (1965).
2. Holtz, P. and Palm, D., Ergeb. Physiol. **58**, 207 (1966).
3. Kirpekar, S. M. and Furchgott, R. F., J. Pharmacol. Exptl. Therap. **143**, 64 (1964).
4. Boura, A. L. A. and Green, A. F., Brit. J. Pharmacol. **14**, 536 (1959).
5. Gokhale, S. D., Gulati, O. D., and Kelkar, V. V., Brit. J. Pharmacol. **20**, 362 (1963).
6. Gillis, C. N. and Nash, C. W., J. Pharmacol. Exptl. Therap. **143**, 1 (1961).
7. Bhagat, B. and Shideman, F. E., Brit. J. Pharmacol. **20**, 56 (1963).
8. Aviado, D. M. and Dil, A. H., J. Pharmacol. Exptl. Therap. **129**, 328 (1960).
9. Anton, A. H. and Sayre, D. F., J. Pharmacol. Exptl. Therap. **122**, 295 (1958).
10. Gaffney, T. E., Circulation Res. **9**, 83 (1961).
11. Hertting, G., Axelrod, J., and Patrick, R. W., Brit. J. Pharmacol. **18**, 161 (1962).
12. Ablad, B., Brogard, M., and Ek, L., Acta Pharmacol. Toxicol. **25**, suppl. **2**, 9–40 (1967).
13. Shanks, R. G., Brit. J. Pharmacol. **26**, 322 (1966).
14. Flacke, J. W., Osgood, P. F., and Bendixen, H. H., Federation Proc. **25**, 471 (1966).
15. Moe, G. K. and Freyburger, W. A., Pharmacol. Rev. **2**, 61 (1950).
16. Gokhale, S. D. and Gulati, O. D., Brit. J. Pharmacol. **16**, 327 (1961).
17. Giachetti, A. and Shore, P. A., Biochem. Pharmacol. **16**, 237 (1967).

Received Nov. 20, 1967. P.S.E.B.M., 1968, Vol. 127.

Effect of Sotalol (MJ 1999) and Propranolol on Insulin-Induced Hypoglycemia in the Rat (32897)

J. H. BROWN AND D. A. RIGGILO
Mead Johnson Research Center, Evansville, Indiana

Propranolol, an adrenergic β-receptor antagonist (1) currently undergoing clinical trials, has been reported to induce hypoglycemic attacks in normal and diabetic patients (2,3). Abramson *et al.* (4) demonstrated a marked reduction of plasma free fatty acid

and glycerol rebound, and a dampening of plasma glucose rebound following intravenous insulin tolerance tests in normal human volunteers treated with propranolol. In addition Bewsher (5) found that propranolol reduced the rise in blood glucose following exercise in man, while Byers and Friedman (6) reported enhancement of insulin-induced hypoglycemia in rats following oral administration of propranolol.

Sotalol, another β-receptor antagonist previously identified in the literature as MJ 1999 (1), resembles propranolol in that it blocks certain metabolic effects of epinephrine and other sympathetic drugs in various animal species and man (1,7). Propranolol, however, differs from sotalol in that it possesses local anesthetic-like (*i.e.*, depressant) actions on the heart (8).

Since sotalol is undergoing clinical trials in disease states or situations thought likely to be affected propitiously by β-adrenergic blockade, it was of interest to compare the effect of this agent with propranolol on insulin-induced hypoglycemia.

Methods. Harlan male rats (130–160 gm) fasted for 18 hours were anesthetized with pentobarbital sodium (30 mg/kg ip) 30 min prior to injection of sotalol or propranolol (20 mg/kg sc). Insulin (Iletin, 1 unit/kg ip) was administered 30 min later [immediately following removal of a blood sample from retro-orbital vessels by means of a capillary pipette] and additional samples were obtained at 1, 2, 3, and 4 hours after insulin. When only β-receptor blocking agents were studied for their effect on blood glucose, samples were taken immediately before and at 1, 2, 3, and 4 hours after drug injection. All test drugs were dissolved in saline and administered in a volume of 2 ml/kg. Blood glucose was determined by diluting whole blood 1:10 with 0.9% NaCl–2% NaF and analyzing the diluted sample in the AutoAnalyzer utilizing the ferricyanide technique (9).

Results. The intraperitoneal injection of insulin (1 unit/kg) in the anesthetized fasted rat produced a moderate hypoglycemia which is significantly enhanced ($p<0.05$) at the 2, 3, and 4 hour intervals by pretreatment with sotalol or propranolol (Fig. 1). Both agents

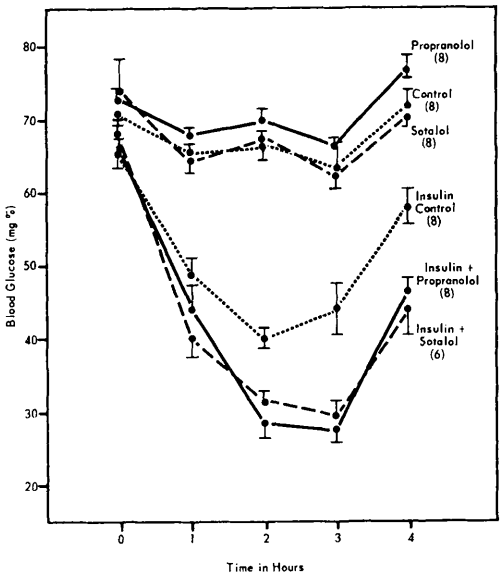

FIG. 1. Effect of sotalol and propranolol on insulin-induced hypoglycemia in the rat. Vertical lines represent ± 1 SEM. Each point is the mean obtained from the number of rats given in parentheses.

were equiactive at the dose tested. However, neither agent altered blood sugar levels when tested alone (Fig. 1).

Discussion. While the mechanism by which sotalol and propranolol enhance insulin hypoglycemia is unknown, several possibilities exist. It has been demonstrated that insulin-induced hypoglycemia results in an increased secretion from the adrenal medulla and that epinephrine is selectively released during this condition (10). Pancreatic insulin secretion is controlled by a number of factors including blood glucose, free fatty acid, and glucagon levels. However, recent studies (11–14) in humans suggest that an adrenergic mechanism is also involved since epinephrine and norepinephrine inhibit insulin release whereas isoproterenol stimulates insulin release. Furthermore, α-receptor blockade antagonizes inhibitory effects of epinephrine, while β-receptor blockade inhibits insulin release by isoproterenol and exaggerates the inhibitory effect of epinephrine (12,15). Therefore, it seems unlikely that sotalol and propranolol enhance insulin hypoglycemia by a mechanism involving reversal of the inhibitory effect of epinephrine on insulin release.

A more likely explanation is that β-adren-

ergic blockade interferes with glycogenolytic and lipolytic actions of catecholamines liberated in response to hypoglycemia thereby counteracting normal homeostatic mechanisms involved in returning blood sugar to normal levels (2,6). Another possibility is that these agents release endogenous insulin as shown by Sussman *et al.* (16) with propranolol in isolated perfused rat pancreas. However, sotalol or propranolol could act synergistically with insulin at its site of action to promote increased glucose uptake by muscle.

That sotalol and propranolol do not alter blood sugar levels *per se* is not surprising since previous work (17) has demonstrated no hypoglycemic effect for sotalol, while the reports on propranolol are conflicting (2–4,6).

The enhancement of insulin by β-adrenergic blocking agents may prove to be a useful effect and perhaps a primary effect of these agents in antagonizing certain of the metabolic actions of catecholamines. However, in view of the clinical results obtained with propranolol (2–4) it is suggested that sotalol be administered with caution to diabetic patients.

Summary. Sotalol and propranolol enhanced insulin-induced hypoglycemia in the rat. Neither agent displayed any significant hypoglycemic activity *per se.*

1. Himms-Hagen, J., Pharmacol. Rev. **19**, 367 (1967).
2. Kotler, M. N., Berman, L., and Rubenstein, A. H., Lancet **2**, 1389 (1966).
3. Mackintosh, T. F., Lancet **1**, 105 (1967).
4. Abramson, E. A., Arky, R. A., and Woeber, K. A., Lancet **2**, 1386 (1966).
5. Bewsher, P. D., Lancet **1**, 104 (1967).
6. Byers, S. O. and Friedman, M., Proc. Soc. Exptl. Biol. Med. **122**, 114 (1966).
7. Svedmyr, N. and Lundholm, L., Life Sci. **6**, 21 (1967).
8. Levy, J. V., Richards, V., Proc. Soc. Exptl. Biol. Med. **122**, 373 (1966).
9. Hoffman, W. S., J. Biol. Chem. **120**, 51 (1937).
10. von Euler, U. S., in "Hormones in Blood," p. 563. Academic Press, New York, 1961.
11. Karam, J. H., Grasso, S. G., Wegrenka, L. C., Grodsky, G. M., and Forsham, P. H., Diabetes **15**, 571 (1966).
12. Porte, D., Jr., Diabetes **16**, 150 (1967).
13. Porte, D., Jr. and Williams, R. H., Science **152**, 1248 (1966).
14. Porte, D., Jr., Graber, A. L., Kuzurja, T., and Williams, R. H., J. Clin. Invest. **45**, 228 (1966).
15. Porte, D., Jr., J. Clin. Invest. **45**, 1057 (1966).
16. Sussman, K. E., Stjernholm, M. R., and Vaughan, G. D., Lancet **1**, 626 (1967).
17. Kvam, D. C., Riggilo, D. A., and Lish, P. M., J. Pharmacol. Exptl. Therap. **149**, 183 (1965).

Received Nov. 20, 1967. P.S.E.B.M., 1968, Vol. 127.

Effects of Prostaglandins E_1, A_1 and $F_{2\alpha}$ on the Coronary and Peripheral Circulations* (32898)

JIRO NAKANO
Departments of Pharmacology and of Medicine, University of Oklahoma School of Medicine, Oklahoma City, Oklahoma 73104

Recently, a family of prostaglandins has been identified and their pharmacological properties have been studied in different species of animals (1–3). However, a few studies (4–6) have been made on the cardiovascular effects of prostaglandins E_1 (PGE_1) and $F_{2\alpha}$ ($PGF_{2\alpha}$). It was found that PGE_1 decreases systemic arterial pressure, whereas $PGF_{2\alpha}$ increases it. The present study was undertaken to investigate the effects of PGE_1, prostaglandin A_1 (PGA_1) and $PGF_{2\alpha}$ on the different regional circulations in dogs.

Methods. Thirty dogs weighing between 20 and 28 kg were anesthetized with sodium pentobarbital (30 mg/kg). In all experiments, the hemithorax was opened under artificial respiration. The pericardium was incised and the heart suspended in a pericardial cradle. Sodium heparin (2.5 mg/kg) was given intra-

* This work was supported in part by research Grants (HE 07334 and HE 08057) from the U. S. Public Health Services.