Action of Hydralazine on Glucose Turnover and Plasma Lipids in Dogs

By SHAFEEK S. SANBAR AND SILVIA A. D. DE ROMERO

Acute effects of a single intravenous injection of hydralazine (20 mg./Kg.) on heart rate, femoral arterial blood pressure, glucose turnover (technique of priming injection-continuous infusion of glucose-U-C^{14}) and plasma lipids and catecholamines were studied in 15 anesthetized dogs. In 6 of the dogs, 3 received isotonic saline solution and 3 received hydralazine diluent. These control dogs had no changes in heart rate, arterial pressure or levels of plasma glucose and FFA. In the others, hydralazine produced significant, prompt and sustained increments in plasma FFA and heart rate and a decrement in diastolic (no change in systolic) blood pressure, the respective mean maximal changes from control levels being 330 Eq./L., 57 x/min., and 26 mm.Hg. Plasma level and rate of appearance (hepatic output) of glucose increased after hydralazine, with a maximum increase in plasma glucose of 58 mg. % above control 2½ hours after injection. Rate of disappearance (tissue uptake) of glucose remained unaltered despite the hyperglycemia. In 3 dogs, high inferior vena cava blood showed marked increases above control levels of both plasma epinephrine and norepinephrine after hydralazine. Plasma cholesterol and triglyceride levels did not change. In conclusion, hydralazine induces hyperglycemia by increasing rate of appearance and by relatively inhibiting rate of disappearance of glucose. The changes in glucose turnover and the noted elevations in plasma FFA and heart rate are paralleled by increased secretion of catecholamines. (Metabolism 18: No. 4, April, 292-299, 1969)

HYDRALAZINE (Apresoline; 1-Hydrazinophthalazine hydrochloride) is an antihypertensive drug which possesses both a central and a peripheral mechanism of action.[1] It produces tachycardia and increases the cardiac output which, according to Moyer and Brest,[1] suggest centrally mediated sympathomimetic activity. Indeed, the drug is ineffective when the vasomotor center is severed from the spinal cord of animals,[2] and its cardiostimulatory effect is inhibited by surgical sympathectomy and by the ganglioplegic drug, hexamethonium.[1] It is well established that hydralazine produces a number of side effects, including gastro-intestinal, cardiac, hematologic, immunologic, skin

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and nervous system manifestations.[1,3] On the other hand, very little is known about the metabolic effects of this drug. Esplugues-Requena and co-workers[4] reported that administration of hydralazine (about 15 mg./Kg.) in dogs induces after 30 minutes from 10.7 to 78.5 per cent increase in carotid arterial blood sugar above initial values, and that a second dose of the drug elicited an even greater hyperglycemia. The authors found no histologic changes in the pancreas at autopsy. Since hydralazine administration appears to stimulate the sympathetic nervous system, it is possible that this drug may secondarily exert an effect on the metabolism of carbohydrates and lipids.

The purpose of this investigation in anesthetized dogs is to delineate the effect of intravenous administration of hydralazine on glucose turnover, using an isotope-dilution technique, and on plasma free fatty acid (FFA), cholesterol, triglyceride, epinephrine and norepinephrine concentrations; systolic, mean and diastolic arterial blood pressure and pulse are also recorded.

Materials and Methods

Fifteen male and female mongrel dogs weighing 11 to 16 Kg. were used in this study. Afer an overnight fast, the dogs were anesthetized with pentobarbital sodium (30 mg./Kg. body weight). A medium-size catheter (Intracath, D. R. Bard, Inc., Murray Hill, N.J.) was inserted in the cephalic vein for intravenous infusions and a polyethylene tube in the femoral artery for repeated blood sampling. The experimental procedures lasted 3 to 4 hours.

After a control period of ½ to 1 hour, 3 dogs received intravenously isotonic saline solution (1 ml./Kg.), 3 received hydralazine diluent (1 ml./Kg.), and 9 received hydralazine (20 mg. Apresoline in 1 ml. diluent/Kg.); the injection was given over a period of about 3 minutes. In 5 of the latter 9 dogs, each serving as its own control, the technic of priming injection-continuous intravenous infusion of tracer glucose-U-C^{14} [5] was utilized to determine the immediate changes in rates of appearance (Ra) and disappearance (Rd) of glucose following intravenous administration of hydralazine. The dose of tracer, calculations of Ra and Rd and laboratory methods were identical to those reported in this journal.[6]

Systolic, diastolic and mean femoral arterial pressure were recorded continuously on a Polygraph (Model M8PM Gilson Medical Electronics, Middleton, Wis.). Beside glucose, plasma was analyzed also for FFA,[7] cholesterol,[8] triglyceride[9] and catecholamines, the latter measured by the trihydroxyindole technique of Lund[10] as modified by Crout[11] and von Euler and Lishajko.[12]

Results

Intravenous injection of isotonic saline solution in 3 dogs (Fig. 1) produced no significant changes in systolic, mean and diastolic blood pressure, pulse, plasma glucose or FFA concentration during the four hour procedure.

Intravenous injection of hydralazine (Apresoline) *diluent* in 3 dogs (Fig. 2) produced a slight and gradual increase in systolic and mean blood pressure, but no changes in diastolic blood pressure, pulse, plasma glucose or FFA concentration.

In contrast, injection of Apresoline in 9 dogs (Fig. 3) did not alter significantly the systolic blood pressure, but it decreased the mean and diastolic blood pressure and increased the pulse throughout the remainder of the procedures. Plasma glucose concentration gradually increased to a maximum of 58 mg. per cent above mean control levels at the end of the procedure. Plasma

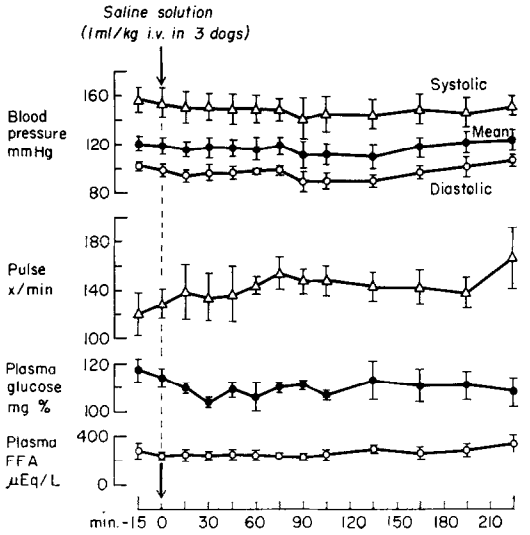

Fig. 1.—Mean ± S.E.M. changes in systolic, mean and diastolic arterial pressure, pulse, and plasma glucose and FFA concentration following saline administration in 3 dogs.

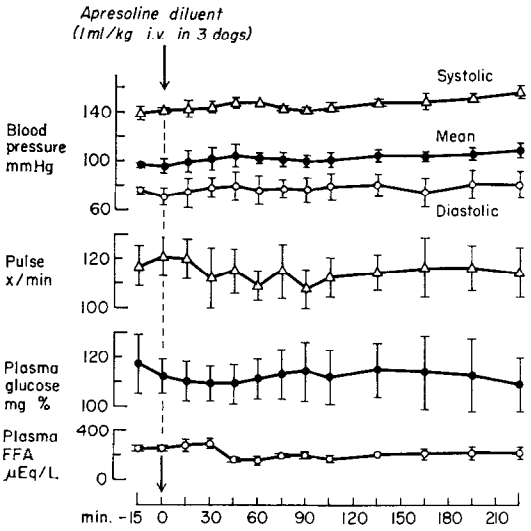

Fig. 2.—Mean ± S.E.M. changes in systolic, mean and diastolic arterial pressure, pulse, and plasma glucose and FFA following administration of hydralazine (Apresoline) diluent in 3 dogs.

FFA concentration almost tripled within 30 minutes after injection of the drug, and it remained elevated until the end of the experiment. In 5 of the 9 dogs (Fig. 4), plasma cholesterol and triglyceride concentrations remained unaltered following hydralazine administration. In these same dogs, the drug produced an increase in rate of appearance (Ra) but no change in rate of disappearance (Rd) of glucose (Table 1); the difference between Ra and Rd accounted for the gradual rise in plasma glucose concentration.

In 3 of the 9 dogs which received Apresoline, plasma catecholamines were measured in blood obtained from the thoracic portion of the inferior vena cava at time 0, 60 and 150 minutes. As shown in Table 2, both the concentrations of plasma epinephrine and norepinephrine were increased after drug injection

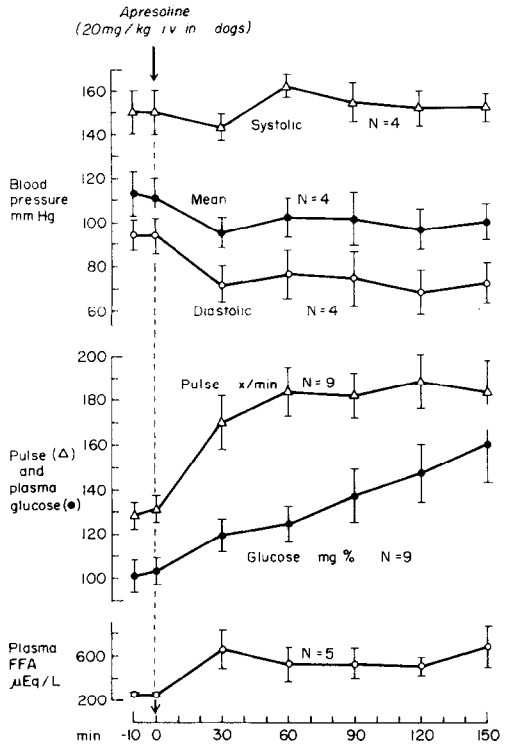

Fig. 3.—Mean ± S.E.M. changes in systolic, mean and diastolic arterial pressure, pulse, and plasma glucose and FFA following hydralazine (Apresoline) administration in dogs.

above control values; the values at 150 minutes were higher than at 60 minutes, which corresponded with the change in plasma glucose concentrations.

Discussion

These studies in dogs confirm the hyperglycemic effect of large intravenous doses of hydralazine (Apresoline), reported previously by Esplugues-Requena et al.[4] It is noteworthy that the hyperglycemia induced by hydralazine is gradual, reaching a maximum at the end of the procedure, 2½ hours after intravenous administration of the drug. It has also been determined isotopically that hydralazine hyperglycemia is associated with a slight increase in rate of appearance of glucose, which represents primarily hepatic glucose output.[13] Furthermore, the rate of disappearance or tissue uptake of glucose remained unaltered despite a substantial hyperglycemia, the mean maximal increase in plasma glucose being 58 mg. per cent. These data indicate, therefore, that both an increment in Ra and a relative inhibition of Rd contributed to the production of hydralazine hyperglycemia.

The data demonstrate further that hydralazine decreases the diastolic arterial pressure and markedly increase the pulse, plasma FFA and catecholamine concentrations. In view of these findings, it is conceivable that the reduction in blood pressure might have triggered the adrenal gland to increase its secretion of catecholamines which in turn influenced the pulse and plasma glucose and FFA metabolism. Such an adrenergic mechanism has been shown to play a

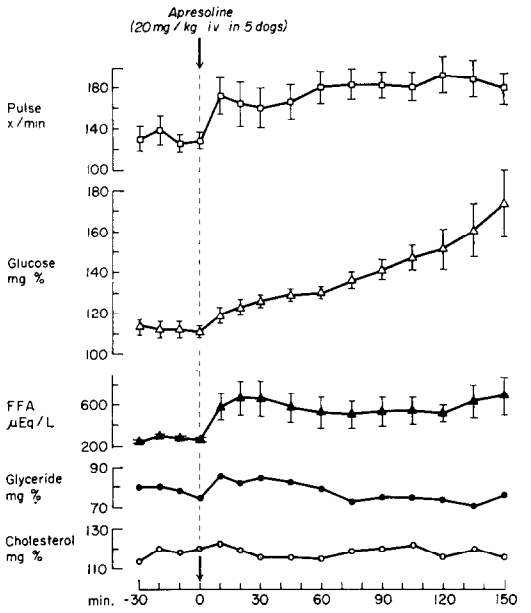

Fig. 4.—Mean (± S.E.M.) changes in pulse and concentrations of plasma glucose, FFA, triglyceride and cholesterol following hydralazine (Apresoline) injection in 5 dogs.

role in the metabolic effects of hypotension induced by hemorrhage[14-15] and by the nondiuretic, benzothiadiazine derivative, diazoxide.[16-18] Similar metabolic changes have also been reported in association with hypotension induced by sodium nitroprusside,[16] trimethaphan camphorsulfonate (Arfonad) and phenoxybenzamine (Dibenzyline)[19] and large doses of diphenylhydantoin (Dilantin) in dogs.[20]

However, it is also possible that the metabolic effects of hydralazine are mediated by direct stimulation of the sympathetic nervous system centrally. As mentioned earlier, the tachycardia induced by hydralazine is inhibited by surgical sympathectomy and by hexamethonium.[1] Furthermore, Gupta and Bhargava[21] have shown that local application of hydralazine over the floor of the fourth ventricle produces tachycardia, that after an intracerebroventricular injection of the drug tachycardia appears prior to hypotension, and that the tachycardia is not prevented by carotid sinus denervation. These data indicate a central site of action of the drug with respect to the tachycardia and hypotension. And it is conceivable that the effects of hydralazine on glucose and FFA metabolism may also be in part centrally mediated. This central nervous system component may act in a manner similar to that of epinephrine by stimulating the so-called "hyperglycemic center" which is situated in the floor of the fourth ventricle, as reviewed recently.[22]

Finally, two other mechanisms should be considered in the action of hydralazine on glucose turnover and plasma FFA concentration. Firstly, the drug itself may possess direct actions on hepatic glucose output, tissue utilization of glucose or adipose tissue lipolysis. Secondly, the alterations in glucose turnover may be secondary to inhibition of insulin secretion by catecholamines[23-25] as well as the increased availability of FFA. And it is possible that hydralazine

Table 1.—Effect of Intravenous Injection of Hydralazine on Mean ± S.E.M. Rates of Appearance (Ra) and Disappearance (Rd) of Plasma Glucose in 5 Dogs

	Before Injection			Determination After Injection of Hydralazine										
	40′	50′	60′	70′	80′	90′	105′	120′	135′	150′	165′	180′	195′	210′
							mg./Kg. Body Weight/min.							
Ra	4.3	4.4	3.8	5.6	4.5	4.6	4.6	4.2	4.8	4.5	4.8	4.8	5.5	5.6
	±.3	±.2	±.1	±.5	±.7	±.3	±.3	±.4	±.2	±.6	±.4	±.8	±.8	±.7
Rd	4.4	4.4	3.9	4.6	4.0	4.2	4.4	4.2	4.2	4.1	4.3	3.9	4.2	4.4
	±.3	±.2	±.0	±.3	±.3	±.4	±.2	±.3	±.1	±.4	±.3	±.2	±.4	±.6
Ra - Rd	—0.1	0.0	—0.1	1.0	0.5	0.4	0.2	0.0	0.6	0.4	0.5	0.9	1.3	1.2

Table 2.—Plasma Catecholamines and Glucose Before and After Hydralazine Injection

Dog No.	Plasma Determination	Before Injection 0′	After Hydralazine 60′	150′
1	Epinephrine (μg./L.)	0.001	0.425	0.550
	Norepinephrine (μg./L.)	0.306	0.798	1.044
	Glucose (mg. %)	67.	79.	81.
2	Epinephrine	0.199	0.260	0.571
	Norepinephrine	0.181	0.373	0.488
	Glucose	86.	92.	98.
3	Epinephrine	0.490	3.048	8.790
	Norepinephrine	0.203	1.055	1.463
	Glucose	84.	136.	212.

itself may directly inhibit insulin secretion. More studies in vivo and in vitro will be required to further elucidate the role that these factors play in the metabolic effects of hydralazine.

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REFERENCES

1. Moyer, J. H., and Brest, A. N.: Hydralazine in the treatment of hypertension. Med. Clin. N. Amer. 45:375, 1961.

2. Craver, B. N., Barrett, W., Cameron, A., and Yonkman, F. F.: Activities of 1-hydrazinophthalazine (Ba-5968), a hypotensive agent. J. Amer. Pharm. Ass. 40:559, 1951.

3. Alarcon-Segovia, D., Wakim, K. G., Worthington, J. W., and Ward, L. E.: Clinical and experimental studies on the hydralazine syndrome and its relationship to systemic lupus erythematosus. Medicine 46: 1, 1967.

4. Esplugues-Requena, J., Brugger-Auban, A., and Castillo-Amoros, E.: La accion hipergluceminate de la apresolina en el perro. Med. Esp. 39:415, 1958.

5. Steele, R.: Influences of glucose loading and of injected insulin on hepatic glucose output. Ann. N. Y. Acad. Sci. 82:420, 1959.

6. Sanbar, S. S.: Effect of L-leucine on glucose turnover in dogs. Metabolism 15: 557, 1966.

7. Dole, V. P., and Meinertz, H.: Microdetermination of long-chain fatty acids in plasma and tissues. J. Biol. Chem. 235: 2595, 1960.

8. Connerty, H. V., Briggs, A. R., and Eaton, E. H., Jr.: Simplified determination of lipid components of blood serum. Clin. Chem. 7:37, 1961.

9. Van Handel, E., and Zilversmit, D. B.: Micromethod for the direct determination of serum triglycerides. J. Lab. Clin. Med. 50: 152, 1957.

10. Lund, A.: Fluorometric determination of adrenaline in the blood. Acta Pharmacol. Kobenhavn 5:231, 1949.

11. Crout, J. R.: Catecholamines, Standard Methods of the American Association of Clinical Chemistry, Vol. III. New York, Academic Press, 1962, pp. 62–79.

12. Euler, U. S. von, and Lishajko, F.: Improved technique for the fluorometric estimation of catecholamines. Acta Physiol. Scand. 51:348, 1961.

13. Hetenyi, G., Jr., Rappaport, A. M., and Wrenshall, G. A.: Effects of insulin on the tracer-determined distribution and production of glucose in liverless dogs. Diabetes 12:150, 1963.

14. Watts, D. T.: Adrenergic mechanisms in hypovolemic shock. *In* Mills, L. C., and Mayer, J. H. (Eds.): Shock and Hypotension. New York, Grune & Stratton, 1965, p. 385.

15. Shoemaker, W. C.: Shock. Springfield, Ill., Charles C Thomas, 1967, p. 120.

16. Staquet, M., Yabo, R., Viktora, J., and Wolff, F. W.: An adrenergic mechanism for hyperglycemia induced by diazoxide. Metabolism, 14:1000, 1965.

17. Tabachnick, I. I. A., Gulbenkian, A., and Seidman, F.: The effect of a benzothiadiazine, diazoxide, on carbohydrate metabolism. Diabetes 13:408, 1964.

18. Sanbar, S. S.: Metabolism of plasma glucose and lipids following diazoxide administration in dogs. Metabolism 16:259, 1967.

19. —, Mitchell, S. A., Lockey, R. F., Vleck, E. A., and Greene, J. A., Jr.: Metabolic effects of hypotension induced by hemorrhage and by hypotensive drugs (abstract). Clin. Res. 15:410, 1967.

20. —, Conway, F. J., Zweifler, A. J., and Smet, G.: Diabetogenic effect of Dilantin (diphenylhydantoin) (abstract). Diabetes 16:533, 1967.

21. Gupta, K. P., and Bhargava, K. P.: Mechanism of tachycardia induced by intracerebroventricular injection of hydralazine (1-hydrazinophthalazine). Arch. Int. Pharmacodyn. 155:84, 1965.

22. Sanbar, S. S.: Alterations in glucose turnover following single intravenous injections of epinephrine and glucagon in dogs. Metabolism 17:631, 1968.

23. Coore, H. G., and Randle, P. J.: Regulation of insulin secretion studied with pieces of rabbit pancreas incubated in vitro. Biochem. J. 93:66, 1964.

24. Kosoka, K., Ide, T., Kuzuya, T., Miki, E., Kuzuya, H., and Okinaka, S.: Insulin-like activity in pancreatic vein blood after glucose loading and epinephrine hyperglycemia. Endocrinology 75:9, 1964.

25. Porte, D., Jr., Graber, A. L., Kuzuya, T., and Williams, R. H.: The effect of epinephrine on immunoreactive insulin levels in man. J. Clin. Invest. 4:228, 1966.