

Propranolol-induced Insulin Release in Isolated Rat Islets of Langerhans

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SUMMARY

Immunoreactive insulin was measured in the medium following incubation of isolated rat islets of Langerhans in different concentrations of propranolol and propranolol plus glucose. Pretreatment with propranolol (20 $\mu\text{g./ml.}$) prevented glucose (3 mg./ml.)-mediated insulin release. Propranolol alone in concentrations up to 25 $\mu\text{g./ml.}$ did not cause insulin release; however, at 50 $\mu\text{g./ml.}$ this drug had strong beta-cytotropic activity. *DIABETES* 22:91-93, February, 1973.

Propranolol, a beta-adrenergic blocking agent, has been associated with reports of clinical hypoglycemia.¹⁻³ Unfortunately, serum insulin levels were not reported in most of the studies so that hypoglycemia secondary to hyperinsulinemia remains a possibility. In one nine-year-old girl intravenous administration of 2 mg. of propranolol caused hypoglycemia only after a twenty-four-hour fast.² Since propranolol did not cause hypoglycemia in this child except under conditions of fasting, it is possible that blockade of hepatic glycogenolysis or gluconeogenesis may have accounted for the hypoglycemia.

In another study using adult healthy volunteers, propranolol was found to decrease the magnitude of postexercise hyperglycemia. The authors interpreted these results as reflecting an inhibition by propranolol of catecholamine-mediated glycogenolysis.⁴ Additional alternative explanations of propranolol-mediated hypoglycemia, however, may include decreased muscle glycogenolysis or adipose lipolysis resulting in decreased available precursors, lactate and free fatty acids, for synthesis of glucose and glycogen in the liver.^{5,6}

Sussman et al. (1967) presented preliminary observations on infusions of the isolated rat pancreas with

propranolol showing that this agent can stimulate insulin release.⁷ The present study corroborates the findings that propranolol can act as a beta-cytotropic agent. Although it is tempting to suggest that release of insulin from beta cells may be an alternative explanation for propranolol-induced hypoglycemia, extreme caution must be exercised in using *in vitro* data to explain *in vivo* events.

MATERIALS AND METHODS

Islets of Langerhans were isolated, as described by Lacy⁸ with minor modifications, from pancreases obtained from male Sprague-Dawley rats weighing 280 to 300 gm. Incubations were carried out in disposable plastic plates containing multiple 3-ml. volume wells (Linbro Chemical Co., Inc., New Haven, Conn.). With the use of a dissecting microscope, five to seven islets were transferred to each well containing 1.0 ml. of modified Krebs-Henseleit buffer⁸ pH 7.4 and incubated for sixty minutes at 37° C. at forty-four oscillations per minute in an atmosphere of 95 per cent oxygen and 5 per cent carbon dioxide. Medium in the control wells contained no glucose. Media in the treatment wells contained glucose (3 mg.) and/or propranolol (5, 10, 15, 20, and 50 $\mu\text{g.}$). In experiments where beta-cytotropic blockade was studied, islets were pretreated with propranolol for twenty minutes and then transferred to another well containing both propranolol and glucose.

A minor modification of the dextran charcoal method of Herbert et al.⁹ was employed to assay immunoreactive insulin in the media. Duplicate 0.1 ml. samples were removed at zero time and again sixty minutes later and the difference in insulin concentrations per well was calculated. Insulin present in control wells (usually only 1 to 4 $\mu\text{U.}$) was subtracted from the insulin concentration in the treatment wells. Thus, variations in animals and in islet preparations were more nearly equalized.

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Accepted for publication September 29, 1972.

RESULTS

Investigations in our laboratory with isolated rat islets of Langerhans show that propranolol can stimulate or inhibit insulin release, depending upon the dose. A glucose concentration of 3 mg./ml. consistently increased insulin concentration in the islet medium above control levels (tables 1 and 2). Pretreatment of the islets with propranolol (20 µg./ml.) for twenty minutes prevented the expected glucose-mediated response (table 2). Lower doses of propranolol (5, 10, and 15 µg.) were inconsistent in providing adequate blockade against glucose-stimulated insulin release; however, these concentrations of propranolol alone did not stimulate insulin release (table 2). Propranolol (20 and 25 µg./ml.) did not stimulate insulin release, but a drug concentration of 50 µg./ml. resulted in greater insulin release than stimulation with glucose (3 mg.) alone (table 1). The combination of glucose (3 mg.) and propranolol (50 µg./ml.) consistently produced more insulin release than glucose alone in the isolated rat islet system. Data showing comparison between propranolol plus glucose and glucose alone on insulin release do not support synergism, and no other conclusions related to receptor specificity can be drawn at this time (table 1).

DISCUSSION

It is difficult to compare concentrations of a drug required to produce a specific biological response be-

TABLE 1
Effect of glucose, propranolol, and glucose plus propranolol on immunoreactive insulin (µU./ml.) released from isolated rat islets expressed as the difference between treatments and controls.

Glucose 3 mg.	Propranolol 50 µg.	Propranolol, 50 µg., plus Glucose, 3 mg.
41	51	46
24	44	49
20	27	65
15	26	63
17	44	58
28	47	70
25	51	30
20	45	41
19	44	34
39	68	—
20	53	—
Mean	Mean	Mean
24.4	45.5	50.7
SE	SE	SE
2.57	3.39	5.21
P*	P*	P*
>0.01	>0.01	>0.01

*Comparison between treatments and control.

tween in vitro and in vivo systems. It is not known what level of propranolol is required to react at the pancreatic beta cell receptor level to alter the rate of insulin release. Some insight may be gained, however, if the change in concentrations of the pharmacologic agent is considered. A twofold increase in propranolol (25 to 50

TABLE 2
Effect of different concentrations of propranolol on release of immunoreactive insulin (µU./ml.) by isolated rat islets expressed as the difference between treatments and controls

Glucose 3 mg.	Propranolol				Propranolol, 20 µg., plus Glucose, 3 mg.
	5 µg.	10 µg.	20 µg.	50 µg.	
34	—	4	3	26	0
24	—	1	2	34	—1
35	2	3	1	35	—1
27	—1	0	—3	47	—1
15	0	1	—6	30	—2
16	0	0	—10	29	—1
56	—1	9	7	—	7
54	6	—10	6	—	—1
39	9	7	3	63	—1
26	4	4	—	50	1
29	4	—2	—	48	—6
Mean	Mean	Mean	Mean	Mean	Mean
32.3	2.6	3.4	0.3	40.2	—0.4
SE	SE	SE	SE	SE	SE
3.88	1.15	1.24	1.73	3.86	1.03
P*	P*	P*	P*	P*	P*
>0.01	NS	NS	NS	>0.01	NS

*Comparison between treatments and control.

$\mu\text{g./ml.}$) is sufficient to replace inhibition with stimulation of insulin release in this system (table 2). Both stimulation and inhibition of the same physiologic response have been reported with other pharmacologic agents.^{10,11} The possibility of a toxic effect causing leakage of immunoreactive insulin from the beta cell at the higher dose cannot be ruled out; however, gross morphologic changes in the islets were not observed with fifty times magnification. Differences of drug doses in this magnitude are frequently encountered in treatment of a single patient under different circumstances or between patients under similar or different circumstances. Thus, conceivably, a dose of propranolol believed to prevent insulin release may, under certain circumstances, stimulate insulin release.

It has been reported that serum insulin concentration is unchanged or possibly decreased following administration of low doses of propranolol (4.8 $\mu\text{g.}$ to 6.9 mg. per hour) to adults under controlled experimental conditions.^{12,13} Additional studies employing higher levels of propranolol, particularly, under situations of carbohydrate deprivation, seem indicated to determine if the magnitude of insulin release is dose-dependent in human beings. The possibility of propranolol acting to stimulate insulin release under conditions of abnormal beta cell function, as in early diabetes mellitus or in adult-onset nonketotic diabetes mellitus, should also be considered. Certainly, more information about serum insulin and glucose levels is necessary before the reasons for propranolol-induced hypoglycemia in some patients will be elucidated.

ACKNOWLEDGMENT

The study was supported by grants no. AM 05760-8

and no. 5TO 1 AMO5105-13. Dr. Northrop is special post-doctoral research fellow USPHS No. TO 1 AMO 5105-12.

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