EFFECT OF ADRENERGIC BLOCKING AGENTS 
ON SYMPATHOMIMETIC AMINES INDUCED 
HYPERGLYCEMIA AND HYPERLACTACIDEMIA

Prabha KHOSLA and K.N. GARG 
Department of Pharmacology, Medical College, Rohtak, Haryana, India 
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Abstract: Sympathomimetic amines epinephrine and isoproterenol were adminis-
tered to dogs, rabbits and pigeons, and effects on blood glucose and blood lactic acid 
levels were studied. Alpha and beta adrenergic receptor blocking drugs were em-
ployed to block the metabolic effects of the amines to elucidate the exact receptor 
status regarding the metabolic actions of sympathomimetic amines on carbohydrate 
metabolism. The results suggest that the receptors associated with hyperglycemic 
response vary depending on the species. In dogs, receptors are of beta type while 
in rabbits and pigeons both alpha and beta type of receptors appear to play a role. 
The hyperlactacidemic response, however, is associated with beta receptors in all 
animals studied herein.

During the last few decades much attention has been focused on the effects of sym-
pathomimetic amines on carbohydrate metabolism. It has been established that the gly-
cogenolytic effect of epinephrine results in a parallel increase in blood glucose and lac-
tate levels (1), derived mainly as a consequence of glycogen phosphorylase in the liver and 
muscle (2-3). The hyperglycemic response has been found to be common to all verte-
brate animals but there are many great variations in sensitivity to these effects depending 
on the species of animal or the sympathomimetic amine used.

The problem of the mode of the effects on carbohydrate metabolism is a controver-
sial one and different views have been put-forward as to whether the action is mediated 
through alpha or the beta receptors. Nickerson and Goodman (4) have shown that 
epinephrine induced hyperglycemia is not blocked by classical alpha adrenergic blocking 
agents such as dibenamine while the ability of DCI, nethalide and phenoxybenzamine to 
block the hyperglycemia in different animals has been reported by other workers (5-8). 
It was also observed that alpha receptor blocking agents have no effect on epinephrine 
induced increase in plasma lactate levels (9).

The exact receptor status of the effects produced by sympathomimetic amines on 
carbohydrate metabolism remains uncertain. The response does not readily fall into the 
alpha or beta type of activity and does not confirm to a consistent pattern. With these 
conflicting reports in mind we have studied the effects of alpha and beta adrenergic block-
ade on the catecholamine induced effects on carbohydrate metabolism in order to elucidate 
the exact receptor mechanism and thus to place the metabolic responses of the sympa-
thomimetic amines on carbohydrate metabolism in proper perspective.
MATERIALS AND METHODS

The study was undertaken in dogs, rabbits and pigeons maintained on a controlled diet. The sympathomimetic amines selected for the study were epinephrine and isoproterenol as the catechol nucleus is necessary for various actions on carbohydrate metabolism. Norepinephrine was excluded on the basis of reports that it has a very poor effect (10). The blocking drugs used were phenoxybenzamine, an alpha adrenergic blocking agent, and propranolol, a beta adrenergic blocking agent.

Healthy adult mongrel dogs of both sexes weighing between 10-20 kg were fasted for about 18 hr before the commencement of the experiment. Administration of sodium pentobarbitone i.v. in a dosage of 30 mg/kg was used for anesthetization. Blood samples were taken from the saphenous vein of which was also employed for i.v. administration of the drugs. The animals were divided into two groups. Control group included 10 animals which were given epinephrine s.c. in the dosage of 0.1 to 0.2 mg/kg. Test group included 15 animals subdivided into 3 sub groups including 5 animals each. The drugs were given as sub group A (Phenoxybenzamine 15 mg/kg i.v. slowly, followed by epinephrine after one hr, B (Propranolol 0.5 to 1 mg/kg i.v., followed by epinephrine after 15 min, and C (Phenoxybenzamine followed after 45 min by propranolol and then 15 min after by epinephrine).

The catecholamines were administered one hr after the administration of phenoxybenzamine, as the peak effect of blockade of alpha receptors is maximal only after one hr (11). On the other hand, propranolol produces effective blockade within 15-20 min, hence the catecholamines were given 15 min after the administration of the blocking drug.

Blood samples were taken in the fasting state and 20 min, 40 min, one hr and 2 hr after the administration of epinephrine and estimations were made for blood glucose and blood lactic acid levels.

Identical procedure was followed with isoproterenol given in equimolar dose of 0.14 to 0.28 mg/kg. The dosage of the drugs is expressed in the form of their respective salts.

Identical experiments were performed in rabbits (weighing 1-2 kg) and pigeons (weighing 200-300 g) except that the marginal ear vein in rabbits and wing vein in pigeons was employed for the collection of blood samples. Further, due to technical difficulties, only three blood samples were collected from pigeons, one fasting and two samples after the administration of sympathomimetic amines at intervals of 30 min and one hr.

Blood sugar was determined by the method of Asatoor and King (12) and lactic acid was estimated by the method of Barker and Summerson (13).

RESULTS

The effects of epinephrine and isoproterenol on blood sugar was observed and the blockade of this response was then determined utilizing various blocking agents in the 1st series of experiments. In the 2nd series, similar experiments were conducted to determine the effects on blood lactic acid. Effects on Blood:- Fasting (control) blood sugar
level in dogs ranged from (in mg/100 ml ± S.E. (Standard error) 87.67 ± 3.6 to 109.99 ± 2.09; in rabbits 80.78 ± 6.29 to 103.27 ± 4.08 and in pigeons 133.36 ± 4.69 to 142.20 ± 3.27.

Significant hyperglycemia was produced both by epinephrine (epi) and Isoproterenol (iso) in all the animals studied. Maximum net blood sugar level was 126.98 ± 10.41 in dogs. The increase was significantly different from control level 87.67 ± 3.6 (P<.01); in rabbits 164.87 ± 12.68 (P<.01) and in pigeons 201.7 ± 10.2 (P<.05). The difference from control level is shown in Figs. (1 to 6).

In dogs, propranolol (Prop) alone (P>.05) as well as in combination with phenoxybenzamine (P>.05) inhibited the hyperglycemic response to epinephrine. Phenoxybenzamine (Phen) alone, however, had no such effect (P<.05) (Fig. 1).

In rabbits and pigeons, neither propranolol nor phenoxybenzamine produced any blockade of epinephrine induced hyperglycemia (P<.05) but when both these blocking agents were given simultaneously an effective blockade (P>.5) was produced (Figs. 3 & 5).
Isoproterenol induced hyperglycemia, however, was effectively inhibited in all three species (P<.05) by propranolol whether given alone or in combination with phenoxybenzamine (Figs. 2, 4 and 6). Effects on blood lactic acid: Control blood lactate level (in mg/100 ml ± S.E. (standard error) was in the range of 7.5 ± 0.24 to 8.3 ± 0.12 in dogs, 7.0 ± 0.58 to 8.4 ± 0.13 in rabbits and 4.7 ± 0.44 to 5.0 ± 0.70 in pigeons.

A significant increase in blood lactate was observed with both the catecholamines in all three species (P<.01). Maximum blood lactate level was 24.9 ± 0.46 in dogs, 23.7 ± 0.31 in rabbits and 9.9 ± 0.85 in pigeons. Phenoxybenzamine did not produce any blockade of this effect (P>.00). Propranolol on the other hand was found to produce an effective blockade (P<.05) (Figs. 1-6).

DISCUSSION

In the present study, significant hyperglycemia and hyperlactacidemia were observed in all three species studied both with epinephrine and isoproterenol. Isoproterenol was found to have almost the same order of potency as epinephrine in dogs, rabbits as well as pigeons. Similar observations were made by Krayer in dogs (14). On the other hand, McChesney et al. (15) found isoproterenol to be less potent than epinephrine in rabbits.

Although the metabolic actions of epinephrine have been well documented, the exact receptor mechanism associated with these actions has not been defined. In our experiments, phenoxybenzamine did not produce any blockade of the catecholamine induced hyperglycemia in any species. Similar findings were reported on dogs using phenoxybenzamine (15, 16), azeptine (17) and dibenamine (4) while in rabbits there were similar observations with dibenamine (18, 19) and priscoline (20).

The beta-adrenergic blocking agent propranolol, however, effectively inhibited this response in dogs. It was observed that propranolol and phenoxybenzamine given simultaneously produce an effective blockade, while the same effect was also produced by propranolol alone. Phenoxybenzamine had no such effect. It can be inferred that in these
experiments, the blockade produced is due to propranolol. Similar observations were made in dogs with other beta adrenergic blocking agents such as DCI (5, 16-17, 21), pro-nethalol and MJ 1999 (22). These findings demonstrate that the hyperglycemic response in dogs is being mediated via the beta receptors.

The situation in rabbits and pigeons is rather complicated as the hyperglycemic response is neither inhibited by phenoxybenzamine nor by propranolol but only when these blocking agents are given simultaneously. It can reasonably be argued that both types of receptors, alpha as well as beta play a part in the hyperglycemic response to epinephrine both in rabbits and pigeons.

The effect of isoproterenol, however, is blocked by propranolol in all species studied. This observation supports the prevalent view that isoproterenol is a beta receptor stimulant and that it produces hyperglycemia by direct stimulation of beta receptors.

It has been postulated that the increase in blood lactate level with catecholamines is derived from muscle glycogen (2, 3, 23). It contributes to hyperglycemia as adrenaline (via 3'-5'-AMP formation) in some way lifts a restriction on the rate limiting step of gluconeogenesis and permits accelerated gluconeogenesis from lactate, and this action is complemented by the simultaneous increase in blood lactate concentration caused by adrenaline (24). Although a rise in the concentration of lactate in the blood does not in itself cause hyperglycemia (25) it does lead to an increase in blood sugar concentration in the presence of adrenaline as lactate uptake by liver, is enhanced by epinephrine (26) which also stimulates gluconeogenesis from lactate (27, 28).

We found that the hyperlactacidemic response was effectively inhibited by propranolol in all three species. The observation is consistent with that of other workers regarding dogs and rabbits (16, 29-30). The effect on pigeons has not been documented. Phenoxybenzamine, on the other hand failed to produce any block in any species. It has been pointed out (5, 9, 16) that attempts to block the hyperlactacidemic response with alpha adrenergic blocking drugs have been largely unsuccessful.

Our observations thus tend to show that there is no species difference as far as the hyperlactacidemic response to catecholamines is concerned. The response was consistently inhibited by propranolol in all three species investigated herein suggesting that this effect on carbohydrate metabolism is mediated via the beta receptors, which presumably are located in the muscle where glycolysis occurs during lactate production (2, 3). The receptors in the liver, however, vary from animal to animal. In dogs they appear to be of beta type whereas in rabbits and pigeons they are assumed to be both alpha and beta type.

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