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DISTURBANCE OF BLOOD GLUCOSE REGULATION IN PERTUSSIS SENSITIZED RATS

By

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It has been previously shown that a decrease in blood glucose and an inhibition of epinephrine induced hyperglycemia was caused by *Bordetella pertussis* vaccine (BPV) treatment in rats (6, 10, 18). BPV is known to increase the sensitivity of rats to anaphylactic shock and to the toxic effects of histamine and 5-hydroxytryptamine (5-HT) (9, 15, 20). Since the severity of anaphylactic shock and of the response to shock-mediators, are considerably influenced by alterations in carbohydrate metabolism (1, 2, 6, 19), BPV-induced changes of blood glucose regulation must play an important role in increased sensitivity of pertussis sensitized rats. The aim of the present study was to examine further details of disturbed blood glucose regulation in BPV treated rats. Experiments were performed to evaluate the influence of BPV pretreatment on hyperglycemic response to catecholamines, cyclic AMP, 5-HT, and histamine.

MATERIALS AND METHODS

Wistar female rats (150-200 g) were maintained on a standard diet, and drinking water was given ad libitum. BPV was administered intraperitoneally in a single dose of 3×10^{10} organisms 4 days prior to blood glucose examinations. Animals were fasted for 18 hours before the determination of plasma glucose levels. All experiments were carried out under pentobarbital anaesthesia except for investigations concerning the effect of 5-HT. Since glycemic response

to 5-HT is considerably influenced by pentobarbital (12) the action of 5-HT on blood glucose was investigated in unanaesthetised rats.

Tail vein blood samples were taken before and 30 min after administration of catecholamines—epinephrine, norepinephrine, isoproterenol (each in a dose of 2 mg/kg s.c.)—10 min after cyclic AMP (20 mg/kg i.v.) or 5-HT (10 mg/kg i.v.) and at various intervals after histamine (10 mg/kg i.v.). In control experiments the effect of phys. saline on plasma glucose concentration was also tested.

Plasma glucose levels were assayed by the ultramicro glucose oxydase (Glucostat, Worthington) procedure of *Cawley et al.* (3). The results were statistically evaluated by Student's one tailed *t*-test.

RESULTS

Similarly to our previous observations (18) BPV alone caused a slight hypoglycemia and completely inhibited the hyperglycemic effect of epinephrine (Table 1). Isoproterenol produced hyperglycemia in normal animals, but did not influence plasma glucose concentration in BPV pretreated rats.

TABLE 1

The Effect of Catecholamines and Cyclic AMP on Plasma Glucose Level in BPV-Treated Rats.

Treatment	Plasma glucose mg % $\pm$ SE			
	Control		BPV treated	
Epinephrine (2 mg/kg s.c.)				
before	101 $\pm$ 5	(9)	88 $\pm$ 8	(6)
30 min after	175 $\pm$ 6*		86 $\pm$ 6	
Norepinephrine (2 mg/kg s.c.)				
before	114 $\pm$ 4	(8)	94 $\pm$ 7	(6)
30 min after	116 $\pm$ 7		91 $\pm$ 7	
Isoproterenol (2 mg/kg s.c.)				
before	111 $\pm$ 6	(9)	93 $\pm$ 4	(11)
30 min after	151 $\pm$ 11**		100 $\pm$ 6	
Cyclic AMP (20 mg/kg i.v.)				
before	106 $\pm$ 6	(10)	86 $\pm$ 4	(10)
10 min after	164 $\pm$ 8*		100 $\pm$ 8	

* $p < 0.001$, ** $p < 0.01$ related to the values obtained before drug administration. Numbers in parentheses represent the number of animals.

Cyclic AMP-induced hyperglycemia was also prevented by BPV. Norepinephrine or phys. saline (the latter is not shown in the table) did not cause any changes, either in control or in BPV treated rats.

Intravenous injection of phys. saline did not elicit a glycemic response even in unanaesthetised animals (Fig. 1), which all goes to show that i.v. injection and vein puncture did not exert a stress reaction influencing blood glucose levels. 10 min after the administration of 5-HT, a considerable increase of blood glucose level could be observed in normal rats. The hyperglycemic response to 5-HT was reversed by BPV pretreatment, i.e., in BPV sensitized animals blood glucose levels were significantly reduced by 5-HT.

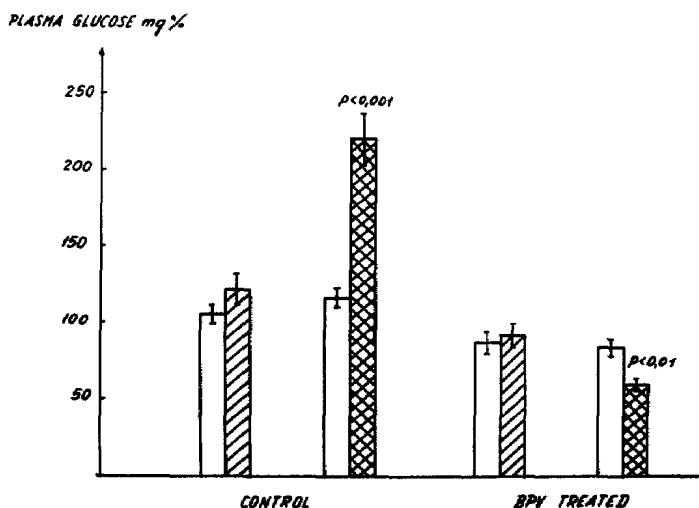


Fig. 1.

The effect of 5-hydroxytryptamine on plasma glucose level in BPV treated rats. □ before treatment, ▨ 10 min after phys. saline, ▩ 10 min after 10 mg/kg 5-HT (i.v.). Results indicate the average of 11 animals and the standard errors. Significance was related to values obtained before treatment.

PLASMA GLUCOSE mg%

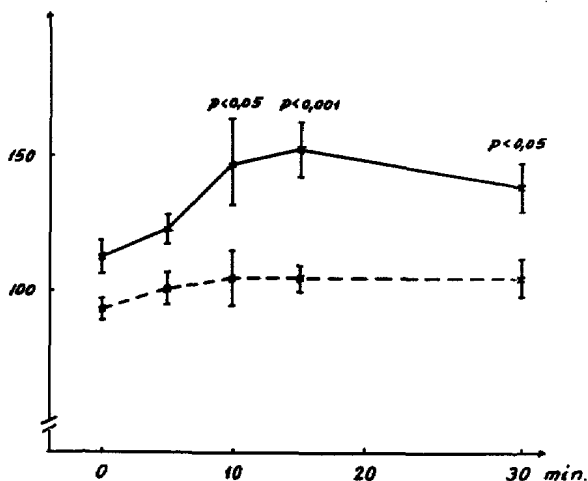


Fig. 2.

The effect of histamine on plasma glucose level in BPV treated rats. x—x control, x----x BPV treated. Results indicate the average of 7 animals and the standard errors. Significance was related to values obtained before histamine treatment.

Histamine induced a moderate hyperglycemia with a maximum after 15 min. Similarly to the above-mentioned drugs, the hyperglycemic effect of histamine was also inhibited by BPV.

DISCUSSION

As known, isoproterenol (16) and cyclic AMP (21), similarly to epinephrine, elicit a hyperglycemic response in rats. BPV pretreatment prevented not only epinephrine but also isoproterenol and cyclic AMP induced hyperglycemia. A diminution of hyperglycemic response to epinephrine was earlier observed by Fishel & Szentiványi, also in BPV treated mice (7). To explain this effect of BPV they suggested that

a blockade of β -adrenergic receptors was elicited by pertussis sensitization (7, 8). However, recent findings regarding the altered regulation of carbohydrate metabolism (10, 13, 18) and insulin release (13, 17) in BPV treated rats are not consistent with the above mentioned theory. Neither did the lack of cyclic AMP-induced hyperglycemia support this hypothesis. According to our present knowledge, two more recent observations seem to offer an explanation for the demonstrated inhibitory action of BPV pretreatment. First, *Kreutner et al.* reported that BPV damages the glycogenolytic system in the liver (13), secondly, following BPV treatment, an increased activity of the insulin secretion mechanism was demonstrated in our previous experiments (17).

In contrast to the other examined hyperglycemic agents the hyperglycemic response to 5-HT was not only completely inhibited by BPV, but a hypoglycemic action of 5-HT could be observed in BPV treated animals. It has been well established that intravenous administration of 5-HT, through its direct action on liver glycogen metabolism, produces hyperglycemia (4, 14). However, the subcutaneous or intraperitoneal injection of this amine elicits a moderate decrease of blood glucose (11). Furthermore, 5-HT-induced hyperglycemia may be preceded by a hypoglycemic phase (12). On the basis of the above-mentioned findings, a twofold action of 5-HT on blood glucose could be presumed. If its hyperglycemic effect has been inhibited by BPV pretreatment, its prevailing hypoglycemic action could result in a decrease of blood glucose.

The mechanism of the hyperglycemic response to histamine is not known. However, a direct or indirect (through the release of catecholamines) glycogenolytic action could be assumed. BPV could exert its inhibitory effect on 5-HT and histamine induced hyperglycemia in the same way as it was assumed in the case of epinephrine. Naturally, more detailed studies will be needed to clarify this problem.

It was already mentioned that alloxan diabetes or the administration of hypertonic glucose solution decrease the severity of anaphylactic shock and the toxic effect of shock

mediators (1, 2, 5, 6). Thus the hyperglycemic action of the released epinephrine and shock mediators may play an important counterregulatory role in these shock states. The inhibition of this counterregulatory mechanism may be one of the factors resulting in the increased sensitivity of BPV-treated rats.

SUMMARY

The hyperglycemic action of epinephrine, isoproterenol, cyclic AMP, and histamine was completely inhibited by BPV pretreatment in rats. Norepinephrine did not influence the plasma glucose level either in normal or in BPV treated animals. 5-HT induced hyperglycemia was reversed by BPV, i.e., in BPV-treated rats it elicited a decrease of plasma glucose. The observed effects of BPV may play an important role in the development of increased sensitivity to anaphylactic shock and shock mediators following BPV sensitization.

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