EFFECT OF ADRENALINE ON THE INDUCTION OF STREPTOZOTOCIN DIABETES

STREPTOZOTOCIN (SZN)[5] is an antibiotic derived from *Streptozotomyces achromogenes*. Chemically, it is 1-methyl-1-nitrosourea derivative of D-glucose[2]. 2-deoxyglucose (2 DG) can protect beta cells against the diabetogenic effect of SZN[2], 2 DG can readily enter cells and be phosphorylated[4]; the product of the phosphorylation diminishes glucose metabolism by inhibition of phosphoglucose isomerase[6] and possibly by reducing glucose uptake[4]. Since adrenaline (ADR) reduces the phosphorylation of 2 DG in skeletal muscle[4], it is of interest to test whether ADR could alter the protective action of 2 DG against SZN diabetes.

The degree of diabetes was assessed by a comparison of the blood sugar curves obtained during glucose tolerance tests (GTT) carried out two days before and one week after treatment with SZN, in male albino rats (200 to 280 g body weight). The procedure for GTT was as follows: Fasting blood sample was taken from animals (fasted for 16 hours), anaesthetised with pentobarbitone (40 mg/Kg subcutaneous), a dose of 1·5 ml of 20% glucose solution per 100 g body weight was administered by stomach tube, and two (hourly) blood samples collected following glucose, from a wound on the tail tip and analysed for glucose[1].

Preliminary experiments showed that: (1) 45 mg/Kg was a suitable dose of SZN for induction of marked diabetes; (2) simultaneous administration of ADR did not affect this action of SZN; and (3) 2DG, administered one week earlier, did not alter the GTT of otherwise normal rats. Three groups of rats received the following treatments, in addition to 45 mg/Kg of SZN administered intravenously in a fresh solution (pH 3·8 to 4·2, concentration 16·7 mg/ml).

Group A: ADR subcutaneously 25 min (100 micrograms) and 10 min (50 micrograms) before SZN.

Group B: 2DG, 1 g/Kg intravenous, in fresh solution (400 mg/ml) 15 min before SZN.

Group C: Both ADR and 2DG together as in above groups.

In Table I, the mean blood glucose values of each group, during GTT before and after treatment, are compared. The "area" under the GTT curve (equal to half of the sum of the blood glucose values at 0 and 120 min *plus* the value at 60 min, in mg hour per 100 ml) is a measure of the glucose tolerance of the animal[3]; the difference in GTT areas before and after treatment (Δ area) in the same animal is an estimate of the degree of diabetes produced by the treatment.

It is seen that SZN produces marked diabetes even in the presence of ADR as indicated by the high Δ area of Group A, in Table I, the values being comparable to those obtained with SZN alone in other experiments in this laboratory. The rats which received 2DG along with SZN (Group B) showed only a small, though significant, Δ area indicating that 2DG affords almost complete protection against the diabetogenic effect of SZN. But, when ADR is given along with 2DG and SZN (Group C), there is a marked Δ area similar to that in Group A. It thus appears that ADR can reduce, if not abolish, the protective effect of 2 DG against SZN.

In view of the fact that ADR does not interfere with the diabetogenic effect of SZN, the demonstrated ability of ADR to annul the protective effect of 2DG is perhaps related to some interaction between 2DG and ADR. Since ADR can interfere with the phosphorylation of 2DG, as it appears in skeletal muscle[4], it may be suggested that 2DG has to be phosphorylated, in order to exert its protective effect against SZN. However, it is difficult to envisage the role of 2DG-6-phosphate in

TABLE I

Group	No. of Rats	Treatment	Blood glucose mg/100 ml during GTT				Area (mg hr/100 ml)	Δ Area (mg hr/100 ml)
			Relation to Treatment	0 min	60 min	120 min		
A	4	Adrenaline + Streptozotocin	Before	95±5	178±27	89±5	257±40	522±162
			After	233±67	469±65	388±101	779±147	
B	5	2-Deoxyglucose + Streptozotocin	Before	93±3	143±25	87±4	248±28	59±19
			After	113±4	128±35	119±9	308±21	
C	4	Adrenaline + 2-Deoxyglucose + Streptozotocin	Before	100±4	163±21	100±4	263±23	390±72
			After	170±24	385±33	394±77	653±63	

All values area: Mean ± Standard Error of Mean. For details of treatment and GTT, *see* text. In paired *t* tests, Δ area was significant ($P < 0·05$) in all three groups.

antagonising the action of SZN, since it is not further metabolised in peripheral tissues[6]; the interference could be at the membrane level, with the uptake of SZN.

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LONG-TERM EFFECT OF NORGESTREL ON BIOCHEMICAL CHANGES IN RAT FALLOPIAN TUBE

NORGESTREL (13 β-ethyl 17 α-ethinyl 19-nortestosterone; Wy 3707) has been reported to be one of the most potent contraceptive progestational steroids[1]. Little is known about the biochemical mechanism of its contraceptive efficacy. However, the biochemical changes in rat uterus under the influence of continuous low dose regimen of this steroid are well demonstrated[2,3]. But meagre attention seems to have been paid to the study of biochemical changes in Fallopian tube under such steroidal administration. The present study deals with the chemical composition of rat Fallopian tube after norgestrel administration under continuous low dose therapy.

Adult healthy albino female rats (Institute's Colony) of regular estrus cycle were administered orally with dl-norgestrel dissolved in olive oil at the dose level of 0·3 μg per rat per day without interruption. The dose of the steroid was calculated on the basis of the human antiovulatory dose[2]. A group of animals was sacrificed at each time intervals of 4, 8 and 12 months after drug feeding along with their respective control group. The animals fed with olive oil served as control. After the completion of scheduled feeding animals were sacrificed and Fallopian tube was carefully dissected out. The biochemical indices were determined in this organ. Protein and glycogen were estimated colorimetrically by the method of Lowry[4] and Montgomery[5] respectively. Lactic acid and acid soluble phosphorus were determined in protein free filtrate as described by Hawk[6].

The protein content of the tissue recorded a decrease due to norgestrel treatment. The decrease was statistically highly significant ($P \leqslant 0{\cdot}01$) at 8 and 12 months treatment period. Glycogen level also registered a significant depletion ($P \leqslant 0{\cdot}05$) throughout the periods of treatment. Likewise, lactic acid content was significantly ($P \leqslant 0{\cdot}05$) diminished. But acid soluble phosphorus remained unaltered as compared to corresponding control values.

The long-term treatment with dl-norgestrel in continuous low dose regimen caused significant decrease in protein content. It has been reported in case of rat[7] and monkey[8] that the Fallopian tube as a component of the reproductive complex is quite sensitive to estrogen and progesterone. Norgestrel has been demonstrated by Edgren[1] to be one of the most potent antiestrogenic steroid. Since estrogen is known to have anabolic effect on its target organs such as uterus and Fallopian tube,

TABLE I

Effect of norgestrel on biochemical changes in rat Fallopian tube (Mean values ± S.E.)

Treatment		Protein (g/100 g)	Glycogen (mg/100 g)	Lactic acid (mg/g)	Acid Soluble Phosphorus (mg/g)
4 month	Control†	19·70±0·70	158·8±12·00	1·58±0·020	0·635±0·042
	treated	17·80±0·20*	115·5±2·00*	0·87±0·21*	0·517±1·02
8 month	Control	16·50±0·64	162·5±2·50	1·18±0·075	0·590±0·024
	treated	12·55±0·41**	135·0±10·00*	016· ±0·090**	0·498±0·034
12 month	Control	22·43±0·52	160·8±7·00	2·08±0·032	0·340±0·041
	treated	17·50±0·65**	130·2±8·40*	1·13±0·038**	0·380±0·038

† Animals served with 1 olive oil only. * Significant at 5% ($P<0{\cdot}05$). ** Significant at 1% ($P<0{\cdot}01$).