EFFECT OF AMITRIPTYLINE ON BLOOD GLUCOSE LEVEL IN RABBITS

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Abstract: Effect of single graded doses of amitriptyline (4, 8 and 16, mg/kg, p.o.) were observed on blood glucose level in 18 h fasted albino rabbits. All the doses of Amitriptyline produced significant hyperglycemia at 4 h, which attained a peak at 24 h with 16 mg/kg dose and appears to be due to blockade of the uptake of monominergic transmitters across the axoplasmic membrane, It (16 mg/kg) also produced glucose intolerance during early hours probably due to interference with gastrin function.

Key words: antidepressant drugs   amitriptyline
            blood glucose level   glucose tolerance test

INTRODUCTION

Long term use of tricyclic antidepressants (TCAs) produces weight gain and a craving for sweets (1). They have inconsistent effect on glucose homeostasis (2-6). Occasional instances of diabetes mellitus, aggravation of existing diabetes, abnormal glucose tolerance, glycosuria and hyperglycemia have been reported after the use of amitriptyline (7) on one hand, while insulin shock, improved glucose utilization as well as hypoglycemic unawareness were reported by other (2, 8, 9). In view of the conflicting reports we have studied the effect of amitriptyline *per se* on glucose homeostasis following acute administration. Further, glucose tolerance test is often performed to detect alterations is glucose utilization in diabetic patients, therefore, its modulation by amitriptyline was also included in the present study.

METHODS

Albino rabbits weighing 1-2 kg were divided in groups of 8-10 animals each, containing equal number of males and females. They were maintained on controlled laboratory conditions and fed on commercial diet ("Gold Mohur",

M/s Lipton India Ltd.). Animals were fasted for 18 h before administering test drug while water was allowed *ad libitum*. Blood samples were collected from the marginal ear vein, before and at 0.5, 1, 2, 3 and 4 h following test drug, for estimating blood glucose level (BGL) by the modified technique of Nelson-Somogyi (10). In one group of rabbits blood samples were collected upto 24 h. Amitriptyline was administered in 3 graded doses (4.0, 8.0 and 16.0 mg/kg, p.o.) through intragastric tube as a single dose for observing its *per se* effect on BGL. The saline fed group served as control. For glucose tolerance test (GTT) amitriptyline (16.0 mg/kg) was administered in close succession to glucose (1.0 g/kg orally as 20% solution) and blood samples were collected before and at 0.5 h intervals for 3 h. Animal data where one or more blood samples could not be collected/estimated for any reason, were excluded form the analysis.

The fasting BGL of each rabbit served its own control and was taken as 100. The change in BGL after the administration of drugs was then expressed as percent BGL. The area under the percent BGL-time curve (AUC) for the blood glucose data of each animal in each experiment was calculated by trapezoid integration between

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0-3 (in GTT studies) and 0-4 or 0-24 h (in other studies). The statistical significance was calculated using unpaired students 't' test.

RESULTS

The blood glucose level (BGL) in the control animals remained fairly constant without any significant, alteration during the observation period of 4 h. The fasting BGL in rabbits of all the groups of this study ranged between 52.1 to 94.9 mg%. Feeding of 4.0 and 16 mg/kg doses of amitriptyline produced significant (P<0.05 and <0.01 respectively) hyperglycemia at 4 h associated with a significant (P<0.05) rise in AUC_{0-4}. However 8.0 mg/kg dose had an initial tendency for hypoglycemia (P>0.05) from 0.5 to 3 h and hence could not alter the AUC_{0-4} inspite of production of significant (P<0.01) hyperglycemia at 4 h (Table I). Highest dose of the drug was selected arbitrarily to study the *per se* effect on BGL for 24 h as well as to observe any alteration in GTT.

The animals of control group exhibited mild hypoglycemia which was maximum at 24 h during the 24 h observation period. Amitriptyline (16 mg/kg) produced a gradual rise in BGL attaining a peak at 24 h with significant hyperglycemia at 3 h and onwards. The

TABLE I : Effect of graded doses of amitriptyline (po) on blood glucose level (BGL) in rabbits. BGL of each animal before drug administration was taken as 100 per cent (Values are mean ± SE).

Drug (mg/kg)	No. of Rabbits	Percent blood glucose level h after drugs					AUC_{0-4}
		0.5	1	2	3	4	
Saline	9	97.3 ± 2.4	97.2 ± 2.1	96.4 ± 2.6	94.9 ± 2.2	93.0 ± 2.3	385.9 ± 5.9
Amitriptyline (4)	8	101.9 ± 1.3	104.6 ± 3.3	104.9 ± 6.3	105.0 ± 3.8	109.2 ± 6.8*	418.9 ± 11.7*
Amitriptyline (8)	8	92.3 ± 4.2	92.5 ± 6.4	92.7 ± 4.2	96.1 ± 2.1	119.3 ± 4.5***	388.9 ± 8.5
Amitriptyline (16)	8	98.7 ± 3.2	99.9 ± 3.7	97.6 ± 2.6	105.8 ± 4.9	106.6 ± 3.6**	406.0 ± 7.1*

*P < 0.05; **P < 0.01; ***P< 0.001 in comparison to saline treated group.

TABLE II : Effect of amitriptyline (16 mg/kg, po) on blood glucose level (BGL) for 24 h and oral glucose tolerance (1.0 g/kg, po) in rabbits. BGL of each animal before drug administration was taken as 100 per cent (Values are mean ± SE).

Drug	No. of Rabbits	Percent blood glucose level h after drugs					AUC_{0-24}
		1	3	5	10	24	
Saline	8	98.9±1.5	95.5±1.7	96.6±1.8	94.8±2.1	93.3±2.9	2,281.2±14.4
Amitriptyline	8	102.8±5.8	107.8±4.9*	109.6±5.6*	120.9±4.7**	142.6±6.6**	2,950.2±22.7**
		0.5	1	1.5	2	2.5	3	AUC_{0-3}
Glucose	8	121.3±2.3	114.9±2.9	110.4±2.3	103.8±1.9	97.8±1.6	95.6±1.5	322.7±4.8
Amitriptyline + glucose	8	169.5±4.5**	148.7±6.4**	113.1±4.8	83.9±2.4**	91.6±3.1	99.5±3.9	353.3±9.3*

*P < 0.05; **P < 0.01 in comparison to respective control group.

AUC_{0-24} of this group was significantly (P<0.001) higher than the control group (Table II).

The animals of the control group exhibited an immediate rise in BGL following glucose administration with peak at 0.5 h followed by a gradual recovery towards base level within next 2 h. Feeding of amitriptyline in close succession to glucose resulted in significant (P<0.001) enhancement of hyperglycemia at 0.5 and 1 h followed by significant (P<0.001) hypoglycemia at 2 h ultimately returning to normal values. The AUC_{0-3} of drug treated group was significantly (P<0.05) higher from that of control GTT (Table II).

DISCUSSION

Modulation of glucose homeostasis resulting in hyper (3, 5) or hypoglycemic responses (2, 4) has been reported from different laboratories with different TCAs. Interestingly amitriptyline exhibited significant hyperglycemic effect (Table I) persisting even up to 24 h with 16 mg/kg dose (Table II). this response of amitriptyline may be produced by potentiation of the actions of catecholamines due to blockade of amine transport system across the axoplasmic membrane (11), or inhibition of serotonin re-uptake (12) imposing an inhibitory regulatory tone on dopaminergic functions (13), and by inhibition of enzyme adenylate cyclase which is thought to resemble the dopaminergic receptors (14), since dopaminergic mechanism has been implicated in the release of insulin from pancreatic beta cell (15). It may be mentioned here that amitriptyline has been shown to inhibit insulin release from rat pancreas (16).

The rise and fall of blood glucose during glucose tolerance test (GTT) is determined by the effect of glucose on insulin secretion due to the presence of anticipatory signals (incretins) from the gastrointestinal tract to the pancreas

(17). Several of the gastrointestinal hormones, including gastrin, have been shown to stimulate insulin secretion (17). TCAs are known to inhibit pentagastrin stimulated gastric acid secretion (18, 19). Since pentagastrin possesses full spectrum of gastric-like activity including stimulation of pancreatic secretion (20), it is not unreasonable to speculate that the observed intolerance to oral glucose in initial hours by amitriptyline is due to some interference in the efficacy of gastrin as an incretin (Table II). Interestingly amitriptyline has been reported to suppress insulin secretion induced by a high glucose stimulus acting through as yet unknown mechanism (21).

However, it is difficult to explain the mild hypoglyoemia in initial hours with 8 mg dose of the drug (Table I) and pro-found hypoglycemia at 2 h during GTT (Table II). Since both hyper as well as hypoglycemia have been reported by different workers (2, 7, 9) it appears that the discrepancy might be due to the differences in the doses employed and the time of blood sample collection for glucose estimation following amitriptyline administration as has been observed in the present investigation.

Thus it may be concluded that amitriptyline disturbs glucose homeostasis and produces undue alterations in GTT. Undesirable fluctuations in BGL may best be avoided by increasing the awareness of those who prescribe and/or monitor the use of amitriptyline. However, further work is essential to delineate the exact mechanism of such alterations in BGL.

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