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The central pharmacological effect of chlorpromazine in rats with alloxan-diabetes

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IN PREVIOUS investigations the authors found that administration of insulin increased the velocity of penetration across cell membranes of many drugs, as well as their tissue level and potency.[1–7] The

problem of whether the action and transport of chlorpromazine (Chl) into the brain tissue is changed in rats lacking insulin, is studied in this paper using alloxan-diabetic rats.

METHODS

The experiments were carried out on 60 Wistar, male rats, weighing 150–250 g. The Chl action was estimated using the conditioned avoidance reflexes. The depressive Chl action was expressed as the per cent decrease in the number of the positive reactions 30 min after administration. The Chl content in the brain tissue was determined according to Dubust and Pascal[8] 30 min after the administration of a dose of 1·7 mg/kg.

Diabetes in rats with fixed conditioned reflexes was induced by intracardial injections of 60 mg/kg of alloxan four to five times every third or fourth day. The experiments were carried out when the blood sugar level was higher than 130 mg per cent. Chl (Fenactil—Polfa) and insulin (Insulinum—Polfa) were injected intraperitoneally. The statistical evaluations were done by the Student's t test.

RESULTS

Influence of Chl on the conditioned avoidance reflexes in rats with alloxan-diabetes

It was found that conditioned reflexes of rats are not changed in diabetes. The Chl administration to healthy rats in the dose range of 1·7, 2·0 and 2·3 mg/kg caused a decrease in the number of positive reactions in proportionally to the increased dose (78 ± 6·88 per cent, 59 ± 12·6 per cent and 52 ± 9·11 per cent).

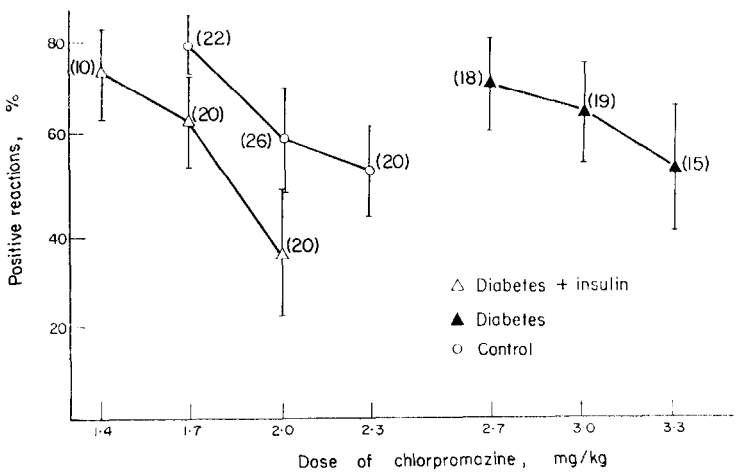

FIG. 1. Influence of chlorpromazine on the conditioned reflexes in rats with diabetes. Figures in parentheses indicate number of experiments.

In diabetic animals the above doses of Chl did not evoke any inhibitory effects. Similar reactions to Chl in diabetic rats (72 ± 7·69 per cent, 68 ± 7·8 per cent and 55 ± 11 per cent were obtained on application of higher doses—2·7, 3·0 and 3·3 mg/kg. The Chl administered with insulin (0·5 U/kg) to diabetic rats in smaller doses (1·4, 1·7 and 2·0 mg/kg) evoked depressive effects similar to those in healthy rats after administration of Chl alone.

The Chl level in the brain tissue of diabetic and healthy rats

It was found that after Chl administration the content in the brain tissue of healthy rats was 9·8 ± 0·5 γ/g, but in rats with diabetes it was only 6·5 ± 0·7 γ/g ($t = 7{\cdot}9$, $P < 0{\cdot}005$). The administration of insulin increases the brain tissue level of Chl to 10·7 ± 1·2 γ/g.

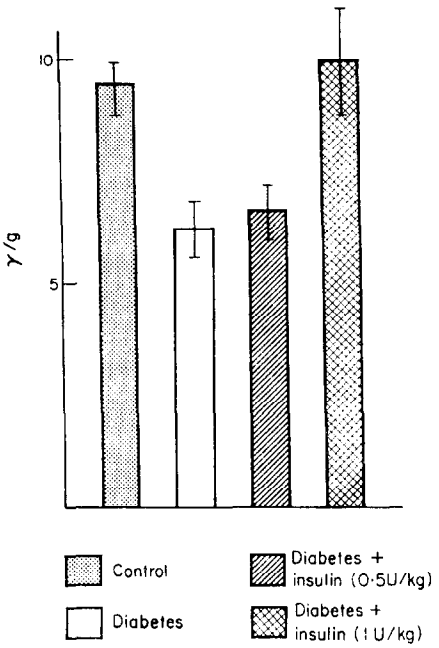

FIG. 2. Chlorpromazine level in the brain tissue of rats with alloxan-diabetes.

DISCUSSION

These experiments provide evidence that Chl depressive effect is decreased in animals with alloxan-diabetes. Similarly ED for Chl in this group of animals is significantly higher than in the healthy rats. The decreased action of Chl was accompanied by a lowered level of Chl in the brain tissue. The insulin administered with Chl to diabetic rats normalized the Chl depressive effect and its level in the brain tissue.

On the basis of results presented and also taking into account our previous investigation[9] we suggest that in diabetes, where there is a deficit of insulin in the organism, the transporting properties of the cell membranes are decreased not only for such substances as some amino acid and carbohydrates[9–13], but also for drugs. This causes the decrease of the Chl penetration to the effector and in consequence causes a decrease in the content of the brain tissue and also a decrease in pharmacological effect.

In conclusion it seems to us that the results confirm our hypothesis that endogenic insulin plays an important role in the transport of the drugs across the cell membranes.

SUMMARY

The action and transport of chlorpromazine into the brain tissue in rats with deficit of insulin (diabetes) was studied. It was found that the depressive effect of chlorpromazine was decreased in animals with alloxan-diabetes. The action of chloropromazine was decreased and accompanied by a lowered level in the brain tissue. The insulin administered with chlorpromazine to diabetic rats normalized the chlorpromazine effect and its level in the brain tissue.

The authors suggest that in diabetes the transporting properties of the cell membranes are decreased for drugs, this causes slow chlorpromazine penetration to the effector and in consequence causes a decrease in the content of the brain tissue and also a decrease in pharmacological effect.

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Absence of isotope effects in the microsomal hydroxylation of acetanilide*

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THE IMPORTANT role played by the hydroxylating enzymes present in liver microsomes in the detoxication of foreign organic compounds is established. In a mechanism study of the conversion of acetanilide to *p*-hydroxyacetanilide, with rabbit liver microsomes, it was shown[1] that molecular oxygen is utilized by the microsomes and is incorporated as the hydroxyl group in *p*-hydroxyacetanilide.

The present study was undertaken to determine whether carbon–hydrogen bond breaking is rate determining in the microsomal hydroxylation of acetanilide. For this purpose *p*-tritioacetanilide was incubated with rabbit liver microsomes and the unreacted acetanilide was isolated and examined for tritium enrichment. In addition, the rate of hydroxylation of pentadeuterioacetanilide was compared with that of unlabeled acetanilide. Prompted by the reports by Guroff *et al.*[2, 3] that the labels are retained in the product after the enzymic parahydroxylation of *p*-tritio- and *p*-deuteriophenylalanine, we also examined the extent of retention of the *para*-tritium in *p*-hydroxyacetanilide after the enzymic hydroxylation of *p*-tritioacetanilide.

EXPERIMENTAL

Acetanilide-4′-H^3_1 (*p*-tritioacetanilide) was prepared by decomposing *p*-aminophenyl-lithium, prepared by the procedure of Gilman and Stuckwisch,[4] with water enriched with tritium (0·25 mc/g). The aniline-NH^3_2-4-H^3_1 was isolated by preparative gas-phase chromatography and then acetylated.

To assess the per cent of tritium in the *para*-position of the synthesized tritioacetanilide, the compound was brominated in acetic acid and the sp. act. of the purified *p*-bromoacetanilide was

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