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SHORT COMMUNICATION

The study on the insulin controlling and directing of chlorpromazine action and level in brain tissue

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THE POTENCY of many drugs depends on their concentration in tissue. Our previous investigations showed that the presence of insulin is one of the factors that increases the velocity of penetration of drugs across cell membranes. The hormone increased both the *in vitro* and *in vivo* level of drugs in tissues[1, 2] and the potency of their action.[2, 3]

It was decided to study the influence of insulin on the potency of chlorpromazine in the hope that some relationship between the action of the latter drug and its concentration in the brain tissue after the administration of insulin could be demonstrated.

Chlorpromazine had been used because of its therapeutical effectiveness when given simultaneously with insulin in hypoglycemic doses in psychiatric clinics. The possibility had to be considered that the potentiation of the pharmacological effects of chlorpromazine does not depend on the insulin-induced hypoglycemia.

MATERIALS AND METHODS

The experiments were carried out on eighty rats weighing 200–300 g. The chlopromazine action was estimated by using the conditioned avoidance reflexes. The depressive chlorpromazine action was expressed as the percent decrease in the number of the positive reactions. The results were estimated on the basis of the mean values obtained from 13–30 experiments (each experiment = 20 reaction). The chlorpromazine content in the brain tissue was determined according to Dubust and Pascal using five or six animals for each point of the curve. Chlorpromazine Fenactil—"Polfa" (0·8 mg/kg) and insulin. Insulinum, "Polfa" (0·5 I.U./kg)—were injected intraperitoneally. The animals receiving insulin were given 0·4 ml of 30% glucose solution into the stomach. This dose normalized the post-insulin hypoglycemia. The statistical evaluations were done by the Student's t-test.

RESULTS

The influence of insulin administered simultaneously with chlorpromazine upon the action of chlorpromazine

Insulin administered with glucose did not influence the conditioned avoidance reflexes (Fig. 1). Chlorpromazine decreased the percentage of the positive reactions to a maximum of 59·0 ± 6·2 per cent (mean of 15 experiments) 30 min after its administration. Chlorpromazine given simultaneously with insulin decreased the percentage of the positive reactions to 38·4 ± 6·9 per cent (mean of 29 experiments). The difference is statistically significant, $t = 10{\cdot}1$, P, 0·001.

The influence of insulin administered simultaneously with chlorpromazine on the chlorpromazine level in the brain tissue

The level of chlorpromazine in the brain tissue 30 min after administration was found to be 20·02 ± 3·31 per cent γ/g_4 (mean of 5 experiments). At the same time the level of this drug in the same tissue in animals receiving the chlorpromazine together with insulin was 49·9 ± 1·0 γ/g_3 (mean of 5 experiments) $t_{3-4} = 21{\cdot}3$, P, 0·001 (Fig. 2).

The influence of insulin administered 20 min after chlorpromazine injection upon the chlorpromazine action

Chlorpromazine decreased the percentage of positive reactions to 58·5 ± 4·6 per cent (mean of 15 experiments) 30 min after administration. Insulin administered 20 min after chlorpromazine increased

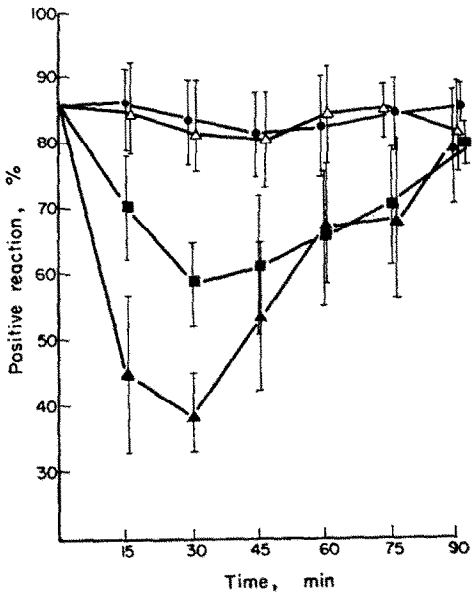

FIG. 1. The influence of insulin administered simultaneously with chlorpromazine upon the action of chlorpromazine on the avoidance reflexes in rats.

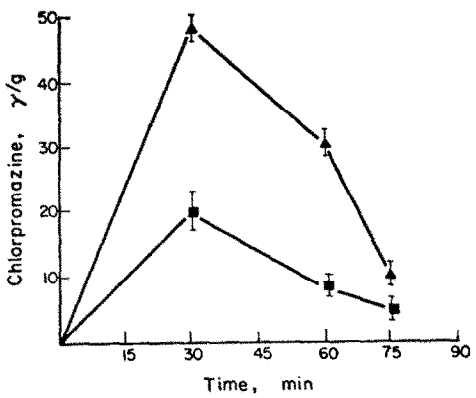

FIG. 2. The influence of insulin administered simultaneously with chlorpromazine on the chlorpromazine level in the brain of the rat.

(10 min after its administration) to about twice the strength of the chlorpromazine action. The percentage of the positive reactions decreased to 38·0 ± 5·4 per cent (mean of 13 experiments) $t = 11{\cdot}8$) P, 0·001 (Fig. 3).

The influence of insulin administered 30 *min after chlorpromazine injection upon the chlorpromazine action.*

Insulin administered at the peak of chlorpromazine action decreased its depressive effect in the next 30 min. The percentage of the positive reactions was 72·7 ± 6·0 per cent (mean of 13 experiments). The control values (chlorpromazine) were 64·0 ± 6·3 per cent (mean of 15 experiments) $t = 3{\cdot}9$, P, 0·01 (Fig. 4).

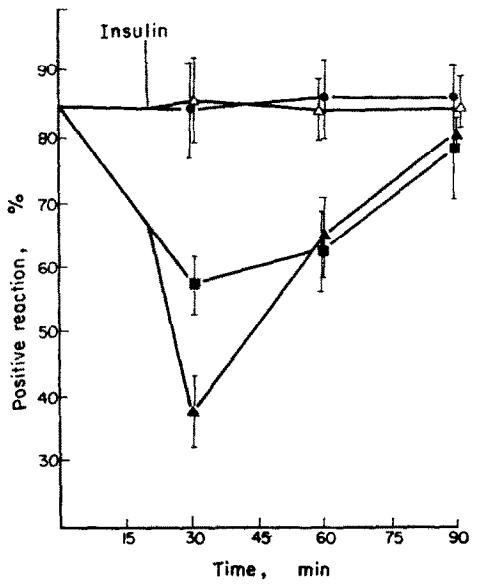

FIG. 3. The influence of chlorpromazine administered 20 min after chlorpromazine injection upon the action of chlorpromazine on the avoidance reflexes in rats.

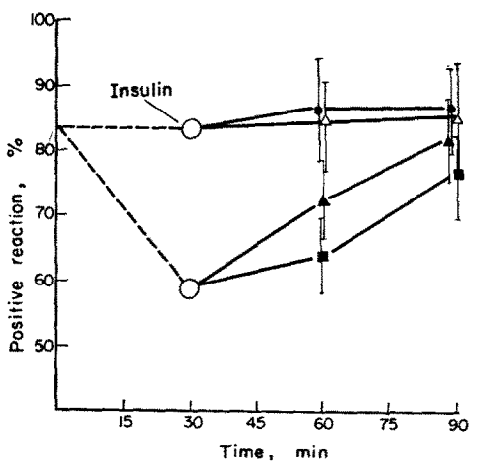

FIG. 4. The influence of insulin administered 30 min after chlorpromazine injection upon the action of chlorpromazine on the avoidance reflexes in rats.

The influence of insulin administered 30 *min after chlorpromazine injection upon the chlorpromazine level in the brain tissue*

Insulin administered at the peak of the chlorpromazine accumulation in the brain tissue decreased the chlorpromazine in the next 30 min. The content of chlorpromazine in the brain tissue of the animals receiving chlorpromazine without insulin was $8{\cdot}16 \pm 1{\cdot}11$ γ/g_9 (mean of 5 experiments and in animals receiving chlorpromazine with insulin was $4{\cdot}22 \pm 0{\cdot}68$ γ/g_{10} (mean of 5 experiments) $t_{9-10} = 6{\cdot}8$, P, 0·01 (Fig. 5).

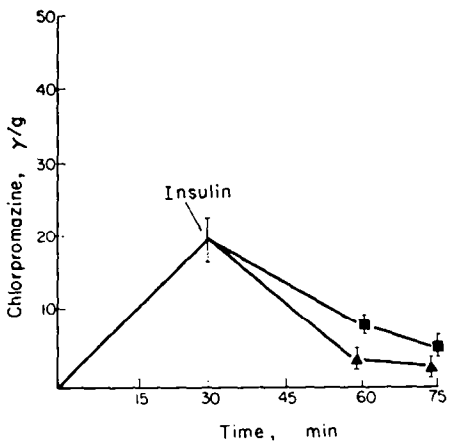

FIG. 5. The influence of insulin administered 30 min after chlorpromazine injection upon the chlorpromazine level in the brain tissue of rats.

DISCUSSION

These experiments provide evidence that insulin administered simultaneously with chlorpromazine increases the potency of the action of chlorpromazine and increases its level in the rat brain tissue. The potentiation of the action of chlorpromazine has been observed only during the first 45 min after the injection of this drug and appeared within 10 min after the injection of insulin. Insulin does not prolong the time of the action of chlorpromazine and at the peak of the chlorpromazine action i.e. 30 min after its injection, insulin has been found to decrease the effect of chlorpromazine in the next 30 min.

The results suggest that the chlorpromazine level in the brain tissue and in consequence the pharmacological effect of this drug can be modified with insulin. It can be supposed that insulin increases the velocity of the penetration of chlorpromazine across cell membranes in both directions. Hypoglycemia does not show any influence on this effect of insulin and it may be concluded that insulin acts directly on cell membranes.

The results allow no conclusion about the precise mechanism of the action of insulin. It is not known whether insulin increases the drug transport across cell membranes or whether it increases the permeability of cell membranes to drugs. Some authors[5-11] suggest that the permeability increasing effect of insulin upon the cell membrane consists on combining its own -S-S groups with -SH groups of the protein of cell membrane. However so far it has not been explained whether insulin does in fact influence the active transport across cell membranes[12-15] or whether it increases the cell membrane's permeability. Our experiments may have a role in therapy since the accumulation of chlorpromazine in the brain tissue and its pharacological effect can be controlled by the simultaneous injection of insulin; the time of chlorpromazine elimination from tissues also can be regulated by insulin administered at the peak of the level of chlorpromazine.

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