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The influence of posterior pituitary hormones on drug passage into the tissue

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OUR PREVIOUS investigations[1–4] indicated that insulin controlled the accumulation of drugs in tissues both *in vitro* and *in vivo* and in this way altered the pharmacological activity of the drugs investigated.[3–4] The transport-stimulating action of insulin towards carbohydrates and amino acids may depend on the presence of disulphide bonds in the molecule.[5–11] PPH has a chemical structure which resembles insulin and Mirsky and Perisulti[12] have found that these hormones stimulated glucose uptake and utilization of fat in the epidymal pad in a similar way to insulin. This paper deals with the influence of PPH on the velocity of INH penetration and distribution and concentration in the tissues.

MATERIALS AND METHODS

Experiments were carried out with 45 rats, each weighing 150–200 g. The drugs were administered intracordially; INH—40 mg/kg, PPH—1 I.U./kg. The INH level in decapitated animals was determined in blood plasma, brain, lung, spleen and kidney at 15, 30, 45 and 60 min intervals after drug injection by the method of Deeb and Vitaglino.[14] For each point plotted 5 or 6 animals were used.

RESULTS

The experimental results are presented in Figs. 1–5. The difference in INH levels at 15, 30 and 45 min—with and without PPH injection—are significant at the 5 per cent level. The figures indicate that PPH administered together with INH increases the maximum level of INH in kidney, lung, brain, and spleen and decreases to less than half the maximum level in the blood plasma. PPH does not prolong the time taken for INH to accumulate in the tissues—the decreased level of INH in blood plasma in animals receiving PPH is probably a secondary effect due to the greater rate of INH penetration into the tissues. PPH initially increase the velocity of the drug penetration into the tissue, but subsequently increases the rate of elimination from the tissues. The effects are most pronounced in the kidney.

DISCUSSION

Previously we have found both *in vivo* and *in vitro* that insulin increased the velocity of INH penetration into lung, brain, liver but was without effect on renal tissue and plasma. Various authors[11, 12, 15, 16] have suggested that both insulin and PPH react through their -S-S groups with

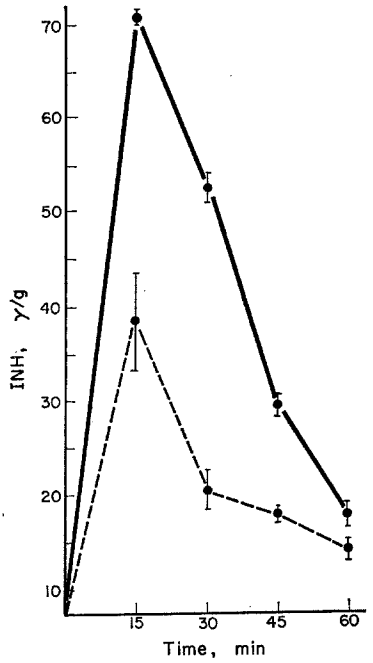

FIG. 1. The influence of PPH on the level of INH in the blood plasma of rats.

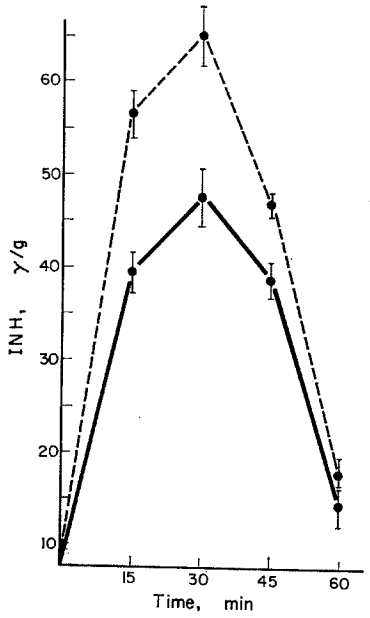

FIG. 2. The influence of PPH on the level of INH in the kidney tissue of rats.

protein-SH groups in the cell membranes thereby increasing permeability to electrolytes and carbohydrates. Molina *et al.* found that vasopressin decreases the concentration of SH groups in the cytoplasm of rat kidney and that this change can be correlated with the antidiuretic effect of this hormone. Orloff and Handler,[17, 18] and Brown *et al.*[19] suppose that binding of vasopressin to renal protein is

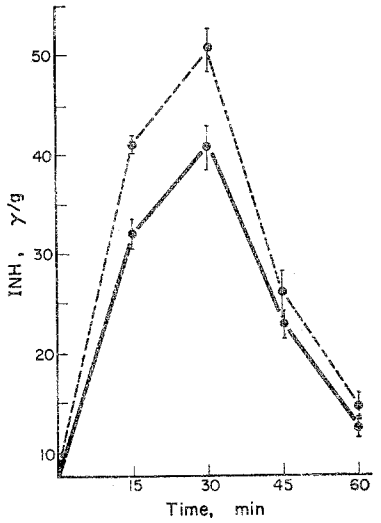

FIG. 3. The influence of PPH on the level of INH in the lung tissue of rats.

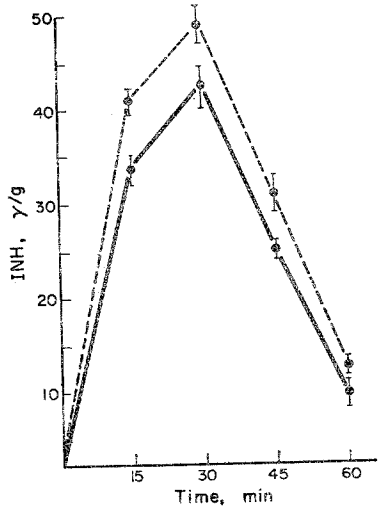

FIG. 4. The influence of PPH on the level of INH in the brain tissue of rats.

responsible for its action of stimulating cyclic AMP formation in the kidney which leads to antidiuretic action. We suppose that this action is non-specific and is connected not only to the increased water or electrolytes movement but also to the action on drug penetration across cell membranes in different tissues and especially the kidney.

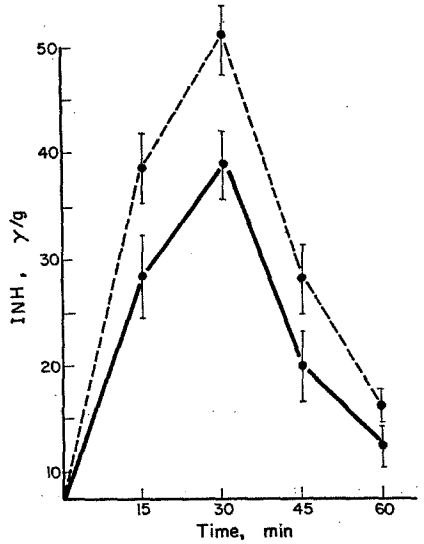

FIG. 5. The influence of PPH on the level of INH in the spleen tissues of rats.

On the basis of the present experiments it is difficult to show whether oxytocin or vasopressin is responsible for the effect on transport. The magnitude of the pharmacological action of many drugs depends on their concentration in tissue. We suppose that by means of PPH and insulin it may be possible to increase pharmacological activity while decreasing toxicity by increasing the rate of elimination of drugs.

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The analysis of changes in the activation energy of succinate dehydrogenase as influenced by some antitumour agents*

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CHANGES in the activation energy of enzymes may bring about marked changes in the metabolism of cells. Many experiments have been carried out dealing with the inhibitory action of alkylating and related agents on enzyme activity[1] but no data are available concerning closer details of enzymic function under the action of such agents, though studies of such type might considerably contribute to the completeness of our concept of cytostatic action which is still unknown at the molecular level as pointed out by Wheeler.[1] Succinate dehydrogenase was chosen for such studies because it had been thoroughly investigated in cancer research and because its activity can be readily determined.[2]

EXPERIMENTAL AND RESULTS

The activity was determined in triplicate using liver homogenates of normal untreated mice[2] at 5 different temperatures, 42, 37, 32, 27 and 22°. Three experiments were made with each substance on 3 different days using the pooled livers of 2 male 'Swiss' mice fasted overnight. 1,000 μg test substance were used per 10 mg wet tissue per ml.

Donor mice were anaesthesized by ether, the chest opened so as to avoid dissection of the internal mammary vessels, right auricle incised and the left ventricle cannulated. The cannula was attached by rubber tubing to a Mariotte flask which was filled with warm physiologic saline and mounted so as to be able to perfuse with an approximate hydrostatic pressure of 120 cm water. After a 3-min perfusion the livers grew maximally pale.

The energy of activation was calculated from 2 velocity constants, obtained at 22 and 42°, from the Arrhenius plot, using the following formula:

$$E = \frac{2{\cdot}303\ (\log k_2 - \log k_1)R}{1/T_1 - 1/T_2}$$

where E is the energy of activation per g mole, k is the specific reaction rate, R is the gas constant per g mole and T the absolute temperature. For details of the calculation see West.[3]

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