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The effects of reserpine on the distribution of [^{14}C]5-hydroxytryptamine in the rat

It has been stated that in the rat, as in many other species, reserpine facilitates the oxidative deamination of both endogenously bound and parenterally administered 5-hydroxytryptamine (5-HT) (Erspamer, 1956a; Garattini, Lamesta & others, 1961; Airaksinen, 1963; Axelrod & Inscoe, 1963; Snyder, Wurtman & others, 1964). The results to be presented in this letter are not entirely consistent with these observations.

Male Wistar rats of 230 $\pm$ 10 g were treated intraperitoneally with reserpine (5 mg/kg) or the vehicle solution (20% ascorbic acid). Eighteen h later they were anaesthetized with pentobarbitone, pithed (Shipley & Tilden, 1947) and given a 1 min infusion of 4·08 μg (4 μCi) of [^{14}C]5-HT creatinine sulphate monohydrate into the femoral vein. At the end of the infusion, a plasma sample and heart and kidney tissues were processed for their total radioactivity and unchanged [^{14}C]5-HT content by the methods previously described (Fozard, 1969). The results are shown in Fig. 1.

There was no significant difference as a result of reserpine pretreatment in the total radioactivity levels of plasma, heart or kidney, or in the unmetabolized [^{14}C]5-HT content of heart and kidney. The small sample of plasma obtainable during the collection period did not allow routine determination of the unmetabolized [^{14}C]5-HT content of the plasma total radioactivity. The tissue to plasma ratios of total radioactivity (Weiner & Trendelenburg, 1962) for the ascorbic acid and reserpine pretreated groups respectively were 0·9 $\pm$ 0·10 and 0·92 $\pm$ 0·13 for hearts and 1·74 $\pm$ 0·24 and 2·14 $\pm$ 0·41 for kidneys.

The rapid metabolism of [^{14}C]5-HT accumulated by hearts and kidneys of reserpine pretreated rats has been shown to be the result of oxidative deamination by monoamine oxidase (Fozard, 1969), and was predictable from the earlier observations of Erspamer (1956a), Airaksinen (1963) and Axelrod & Inscoe (1963). However, in the present work an unexpected finding was that the results obtained in animals given reserpine were not significantly different from those obtained in the vehicle-pretreated controls. The explanation may be related to the dose of 5-HT used and its mode of administration.

Both Erspamer (1956b) and Airaksinen (1963) demonstrated that in normal rats the proportion of a small dose of amine excreted as 5-hydroxyindoleacetic acid was greater than that excreted from a larger dose. Airaksinen (1963) found the proportion of deaminated metabolites when 5-HT was given subcutaneously or by slow intravenous injection was greater than when given by rapid intravenous injection. In his experiments, pretreatment with reserpine increased the amount of 5-hydroxyindoleacetic acid after intravenous injection of 5-HT such that the difference usually observed

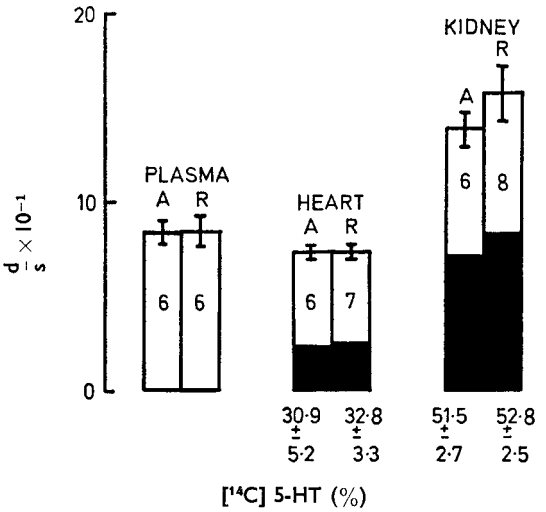

FIG. 1. The distribution of radioactivity after infusion of 4·08 μg (4 μCi) of [14C]5-HT creatinine sulphate monohydrate into reserpinized pithed rats (R) and pithed rats treated with the vehicle solution of 20% ascorbic acid (A). The histograms show the mean total radioactivity in disintegrations per 0·1 s per ml of plasma or per g of heart or kidney tissue with standard errors. The proportion of the total radioactivity which is present as the unchanged [14C]5-HT is represented by the solid portion of the histogram. The actual percentages with standard errors are given below each histogram.

between subcutaneous and intravenous administration with respect to 5-hydroxyindoleacetic acid excretion was annulled. In the present experiments the effect of slowly infusing a small dose of [14C]5-HT by the intravenous route can be equated with the concept of a slow leaching of a larger dose from a subcutaneous depot. Therefore one might expect not only the rapid extensive metabolism of [14C]5-HT by deamination, but also a lack of difference between normal and reserpinized animals in this respect. Such a suggestion would also explain the inconsistency between the present results and those reported by Axelrod & Inscoe (1963), where pretreatment of rats with reserpine (5 mg/kg) increased the metabolism and reduced the tissue concentrations of a larger dose (250 μg) of [14C]5-HT after rapid intraveous injection.

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May 13, 1969

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