predominant radioactive spot corresponding to perphenazine sulfoxide carrier. Low levels of radioactivity on paper strips precluded the quantitative evaluation of results (high lipid concentration in the methanolic extracts greatly limited the volume of sample that could be spotted on the paper).

The difference between the liver and brain tissues in extractability and chemical form of the radioactive material may indicate different metabolic fates of perphenazine in these tissues. This seems to be further substantiated by analysis of subcellular distribution of radioactivity, as illustrated in Fig. 2. The results show a clear difference in the distribution pattern at 1 hr; of interest, however, are the marked, but opposite, changes occurring in liver and brain at later time intervals.

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## Demethylation of imipramine in male and female rats

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IMIPRAMINE is structurally related to the phenothiazine derivatives currently in wide use as tranquilizing agents; it has an ethylene linkage substituted for the sulfur bridge. Imipramine, however, produces primarily antidepressant effects in patients with depression, although only sedative or tranquilizing actions are found in nondepressed patients.[1] In addition, the antidepressant actions are manifest after a variable period of medication, sometimes a matter of 1 or 2 weeks. Recently Gillette *et al.*[2] and Sulser *et al.*[3] have suggested that both the delayed onset of action of the drug and its antidepressant properties may be ascribed to the formation of the demethylated derivative, desmethylimipramine. This report confirms their observations on the metabolism of the drug in the rat and demonstrates, in addition, a sex difference in the rate of conversion of imipramine to desmethylimipramine.

Imipramine (40 mg/kg) was administered intraperitoneally to male and female rats of the Wistar strain. At various times after injection the brains were removed, frozen on solid carbon dioxide, and subsequently analyzed for their content of imipramine and desmethylimipramine by the method described by Gillette *et al.*[2] for the isolation of desmethylimipramine from rat brain. The compounds were extracted from alkaline brain homogenates with heptane containing 1·5% isoamyl alcohol, the heptane washed with 0·1 N NaOH and the desmethylimipramine and imipramine extracted back into an aqueous phase with phosphate buffer pH 5·9 and 0·1 N HCl, respectively. The fluorescence (activation 295 mμ, fluorescence 415 mμ) of the final extracts in 0·39 N NaOH provided a measure of the amount of each amine. As a routine measure to improve the separation of the two phases, the extracts were frozen after each extraction prior to centrifugation. Standards were included in each set of determinations.

The results given in Table 1 show that appreciable conversion of imipramine to desmethylimipramine occurred in both male and female rats; 1 hr after injection the brain concentration of desmethylimipramine was much greater in males than in females, while at 4 hr the concentration was about the same in both sexes. The female rats, therefore, exhibit a slower rate of demethylation of imipramine at 1 hr only. It is possible that a sex difference also exists in the further metabolism of desmethylimipramine. It may be noted that at both time intervals the ratio of precursor to product was higher in the male than in the female. Sulser *et al.*[3] found comparable ratios and absolute concentrations of these drugs in rats receiving both imipramine and Ro-4-1284, a benzoquinoline derivative. They also noted a considerable difference in the rate of metabolism of imipramine in two different strains of rats.

TABLE 1. CONVERSION OF IMIPRAMINE TO DESMETHYLIMIPRAMINE IN RAT BRAIN

| Sex | No. of animals | Hr after injection | Imipramine* ($\mu$g/g $\pm$ s.e.) | Desmethylimipramine ($\mu$g/g $\pm$ s.e.) | Ratio: Imipramine Desmethylim. |
|---|---|---|---|---|---|
| Male | 11 | 1 | 15·6 $\pm$ 1·0 | 12·1 $\pm$ 1·0 | 1·30 |
| Male | 27 | 4 | 6·0 $\pm$ 0·4 | 8·8 $\pm$ 0·6 | 0·68 |
| Female | 8 | 1 | 15·1 $\pm$ 2·4 | 5·8 $\pm$ 0·8 | 2·60 |
| Female | 36 | 4 | 9·4 $\pm$ 0·5 | 9·4 $\pm$ 0·6 | 1·00 |

* Wistar strain rats (200–400 g) were injected intraperitoneally with 40 mg imipramine/kg.

These results show that the brain concentration of both desmethylimipramine and imipramine may vary greatly with the sex and strain of rat used for study and suggest that the psychoactive effects of these drugs may be dependent upon the interaction of several physiological and metabolic factors.

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## Über der Mechanismus der Narkosebeeinflussung durch Iproniazid

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ERSTE pharmakologische Untersuchungen des Iproniazid (Isopropylisonicotinsäurehydrazid, IPN) hatten ergeben, daß diese Substanz eine nachfolgende Hexobarbitalnarkose verlängert.[1] Es lag nahe, diese Wirkung auf die Hemmung der Monoaminoxydase durch IPN und die daraus resultierende Anhäufung von biogenen Aminen im ZNS zurückzuführen. Es konnte aber gezeigt werden, daß IPN auch den Hexobarbitalabbau in den Lebermikrosomen hemmt,[2] so daß die Narkoseverlängerung durch die verlangsamte Elimination des Barbiturats erklärt wurde. Andererseits zeigte sich, daß die narkoseverlängernde Wirkung des IPN nur in den ersten 6 bis 10 Stunden deutlich nachweisbar ist. 12 bis 16 Stunden nach der Applikation von IPN geht die Narkoseverlängerung aber in eine Narkoseverkürzung über.[3] Da auch die Anreicherung der Amine erst allmählich erfolgt, war es durchaus